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James S. Richter

Attorneys for Defendants Somerset Therapeutics, LLC, Somerset Pharma, LLC, Odin Pharmaceuticals, LLC Apotex Inc. and Apotex Corp.,

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AMERICAN REGENT, INC.,	:	Honorable Brian R. Martinotti, U.S.D.J.
Plaintiff,	:	Civil Action Nos. 24 CV 1022 (BRM)(CLW)
v.	:	24 CV 1030
	:	24 CV 1169
SOMERSET THERAPEUTICS, LLC, SOMERSET PHARMA, LLC, ODIN PHARMACEUTICALS, LLC, APOTEX INC., APOTEX CORP., RK PHARMA, INC. and ACCORD HEALTHCARE, INC.,	:	24 CV 2268
	:	24 CV 9600
	:	(Consolidated)
Defendants.	:	**DECLARATION OF JAMES S. RICHTER SUBMITTED IN SUPPORT OF DEFENDANTS' OPENING MARKMAN BRIEF**

JAMES S. RICHTER, of full age, hereby declares as follows:

1. I am an attorney at law of the State of New Jersey and Of Counsel to Midlige Richter LLC, attorneys for Defendants, Apotex Inc., Apotex Corp., Somerset Therapeutics, LLC, Somerset Pharma, LLC, and Odin Pharmaceuticals, LLC in the above-captioned matter.

2. This Declaration is submitted in support of Defendants' Opening *Markman* Brief.

3. Attached hereto as Exhibit "A" is a true copy of U.S. Patent Application No. 17/365,695, Preliminary Amendment Claims dated August 1, 2021.

4. Attached hereto as Exhibit "B" is a true copy of U.S. Patent Application No. 17/365,695, Final Rejection dated August 7, 2022.

5. Attached hereto as Exhibit "C" is a true copy of U.S. Patent Application No. 17/365,695, Applicant Amendment Claims dated October 7, 2022.

6. Attached hereto as Exhibit "D" is a true copy of U.S. Patent Application No. 17/365,695, Non-Final Rejection dated October 26, 2022.

7. Attached hereto as Exhibit "E" is a true copy of U.S. Patent Application No. 17/365,695, Applicant Amendment Claims dated April 26, 2023.

8. Attached hereto as Exhibit "F" is a true copy of U.S. Patent Application No. 17/365,695, Applicant Remarks dated April 26, 2023.

9. Attached hereto as Exhibit "G" is a true copy of U.S. Patent Application No. 17/365,695, Notice of Allowance dated May 24, 2023.

I hereby declare under the penalty of perjury that the foregoing statements made by me are true and correct.

s/ James S. Richter

James S. Richter
jrichter@midlige-richter.com

Dated: April 18, 2025

EXHIBIT A

IN THE CLAIMS:

1. (Original) An injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

2. (Original) The injectable composition of claim 1, wherein the injectable composition comprises 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition.

3. (Original) The injectable composition of claim 1, wherein the injectable composition comprises 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per 1 mL of injectable composition.

4. (Original) The injectable composition of claim 1, further comprising (i) iodine from about 0.0001 to about 0.2 mcg/kg/day, fluoride from about 0.0001 to about 2.7, aluminum from about 0.0001 to about 0.6 mcg/kg/day or a mixture thereof; or (ii) iodine from about 0 to about 0.2 mcg/kg/day, fluoride from about 0 to about 2.7, aluminum from about 0 to about 0.6 mcg/kg/day or a mixture thereof.

5. (Original) The injectable composition of claim 1, further comprising (i) iron from about 0.0001 to about 10 µg/mL, silicon from about 0.0001 to about 100 µg/mL, magnesium from about 0.0001 to about 50 µg/mL, calcium from about 0.0001 to about 50 µg/mL, boron from about 0.0001 to about 50 µg/mL or a mixture thereof; (ii) iron from about 0 to about 10 µg/mL, silicon from about 0 to about 100 µg/mL, magnesium from about 0 to about 50 µg/mL, calcium from about 0 to about 50 µg/mL, boron from about 0 to about 50 µg/mL or a mixture thereof; or (iii) wherein the zinc is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection.

6. (Original) The injectable composition of claim 1, wherein the composition has a pH of about 1.0 to about 5.

7. (Original) The injectable composition of claim 6, wherein the composition further comprises a pH adjusting agent to adjust the pH.

8. (Original) The injectable composition of claim 1, wherein at least one of the zinc comprises about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises about 0.03 wt. percent to about 0.13 wt. percent, the manganese comprises about 0.0055 wt. percent to about 0.013 wt. percent, the selenium comprises about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 99.66 wt. percent based on a total weight of the injectable composition.

9. (Original) The injectable composition of claim 8, wherein at least one of the zinc comprises about 0.3 wt. percent, the copper comprises about 0.03 wt. percent, the manganese comprises about 0.0055 wt. percent, the selenium comprises about 0.006 wt. percent, or the water comprises from about 99.66 wt. percent based on a total weight of the injectable composition.

10. (Original) The injectable composition of claim 1, wherein the injectable composition is at least one of a preservative-free composition, a sterile composition, or a ready-to-use injectable aqueous composition.

11. (Original) The injectable composition of claim 1, wherein the injectable composition comprises a preservative.

12. (Original) The injectable composition of claim 11, wherein the preservative comprises benzyl alcohol in an amount of 0.9 % by weight based on a total weight of the injectable composition.

13. (Original) The injectable composition of claim 5, wherein the elemental zinc is from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is from cupric sulfate or cupric sulfate pentahydrate, the elemental manganese is from manganese sulfate or manganese sulfate monohydrate and the elemental selenium is from selenious acid.

14. (Original) The injectable composition of claim 1, wherein the injectable composition is in a multi-dose vial.

15. (Original) The injectable composition of claim 14, wherein the multi-dose vial contains 10 mL of the injectable composition.

16. (Original) The injectable composition of claim 1, wherein the injectable composition further comprises about 0.0001 µg/mL to about 0.25 µg/mL of chromium.

17. (Original) The injectable composition of claim 1, wherein the injectable composition contains about 1 ppm to about 6 µg/mL of aluminum.

18. (Original) The injectable composition of claim 1, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.3 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.015 to about 0.08 mg/day, and the selenium is selenious acid at a dose of about 20 to about 60 µg/day.

19. (Original) The injectable composition of claim 1, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.5 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.15 to about 0.8 mg/day, and the selenium is selenious acid at a dose of about 20 to about 40 µg/day.

20.- 55. (Cancelled)

56. (Original) A method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about

40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

57.- 64. (Cancelled)

65. (Original) An injectable trace element composition comprising water, about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

66. (Original) The injectable composition of claim 1, wherein zinc comprises from about 800 µg to about 4000 µg per 1mL of the injectable composition.

67. (Original) The injectable composition of claim 1, wherein copper comprises from about 40 µg to about 400 µg per 1mL of the injectable composition.

68. (Original) The injectable composition of claim 1, wherein selenium comprises from about 4 µg to about 90 µg per 1mL of the injectable composition.

69. (Original) The injectable composition of claim 1, wherein manganese comprises from about 1 µg to about 80 µg per 1mL of the injectable composition.

70. (Original) The injectable composition of claim 1, wherein the zinc, copper, selenium, manganese are in elemental or salt form.

71. (Original) The injectable composition of claim 7, wherein the pH adjusting agent is at least sodium hydroxide or sulfuric acid.

72. (Original) A method of maintaining, supplementing or increasing one or more trace elements to a patient in need thereof, the method comprising administering to the patient about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or

about 1 µg to about 80 µg of manganese per about 250 mL to 4000 mL of aqueous fluid, the aqueous fluid comprising an amino acid, a dextrose, a lipid, an electrolyte or a mixture thereof.

73. (Cancelled)

74. (Original) The injectable composition of claim 1, wherein the injectable composition contains less than about 0.25 µg/mL of chromium.

75. (Original) The injectable composition of claim 1, wherein the permitted daily limits (PDL) of the injectable composition do not exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of calcium, about 10 µg/ day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

EXHIBIT B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/365,695	07/01/2021	Gopal Anyarambhatla	1848-32 US	8197

109802 7590 07/07/2022

Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

EXAMINER	
SOROUSH, ALI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
07/07/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

npinou@slsllp.com
smoon@slsllp.com
wschmidt@slsllp.com

Office Action Summary

Application No.	Applicant(s)		
17/365,695	Anyarambhatla et al.		
Examiner	**Art Unit**	**AIA (FITF) Status**	
ALI SOROUSH	1617	Yes	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 05/25/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-18,56,65-72 and 74-75 is/are pending in the application.

5a) Of the above claim(s) 56 and 72 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-18,65-71 and 74-75 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 05252022, 06022022, 06152022.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Acknowledgement of Receipt

Applicant's response filed on 05/22/2022 to the Office Action mailed on 02/25/2022 is acknowledged.

Claim Status

Claims 1-18, 56, 65-72, and 74-76 are pending.

Claims 55 and 57-64 were previously cancelled and claim 19 is cancelled.

Claims 56 and 72 are withdrawn as being directed to a non-elected invention.

Claim 1, 4, 5, 16, 17, 65-69 and 75 are currently amended.

Claims 1-18, 65-71, and 74-76 have been examined.

Claims 1-18, 65-71, and 74-75 are rejected.

Priority

Priority to application 63/047708 filed on 07/02/2020 is acknowledged.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 05/25/2022, 06/02/2022 and 06/15/2022 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Withdrawn Claim Rejections - 35 USC § 112

Response to Applicant's Arguments

The rejection of claims 4 and 75 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention is withdrawn in view of the amendments to the claims.

The rejection of claims 66-69 under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends is withdrawn in view of the amendments to the claims.

Withdrawn and New Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Response to Applicant's Arguments

The rejection of claims 1, 4, 5, 8-11, 66, 70, 74, and 75 under 35 U.S.C. 102(a)(1) as being anticipated by Chang et al. (US Patent Application Publication 2015/0238527 A1, Published 08/27/2015) is withdrawn in view of the amendment to the claims.

This is a new ground of rejection necessitated by the amendment to the claims

Claim(s) 1, 4-8, 10-15, 17, 18, 65-71, and 75 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019).

The claims are directed to an injectable aqueous composition comprising water, 800-4,000µg/ml of zinc, preferably elemental zinc, more preferably zinc sulfate heptahydrate, 40-400µg/ml copper, preferably elemental copper, more preferably cupric sulfate, 1-80µg/ml manganese, preferably elemental manganese, more preferably manganese sulfate, and 4-90µg/ml selenium, more preferably elemental selenium, and most preferably selenious acid; wherein the composition is a sterile composition. The claims are further directed to the composition has a pH of about 1.0-5. The claims further comprise a pH adjusting agent such as sodium hydroxide and/or sulfuric acid. The claims are further directed to the composition comprising a preservative. The claims are further directed to the composition comprising as the preservative benzoyl alcohol in an amount of 0.9% based on the total weight of the composition. The composition further comprises iodine from about 0-0.2 mcg/kg/day, fluoride from about 0-2.7, aluminum from about 0-0.6 mcg/kg/day or a mixture thereof. The composition further comprises iron from about 0-10 µg/ml, silicon from about 0-100 µg/ml, magnesium from about 0-50 µg/ml, calcium from about 0-50µg/ml, boron from about 0-50µg or mixtures thereof. The claims are further directed to the composition wherein the permitted daily limits (PDL) of the

injectable composition do not exceed for example about 0.4µg/day of cadmium. The claims are further directed to the composition being in a multi-dose vial comprising 10mL of the composition.

Drugs.com teach Multitrace-5 is a sterile nonpyrogenic solution trace element injection for total parenteral nutrition (Page 1, Multitrace-5 Description). Each mL comprises 1000µg zinc, 400µg copper, 100µg manganese, 4µg chromium, 20µg selenium, 0.9% benzyl alcohol preservative, sulfuric acid and/or sodium hydroxide for pH adjustment, and water for injection in 10mL multiple dose vial (Page 3, Container). The ingredients are zinc sulfate heptahydrate, cupric sulfate, manganese sulfate, chromic chloride, selenious acid, benzoyl alcohol, sulfuric acid, sodium hydroxide, and water (page 4, Ingredient Name). The suggested dosage level of zinc is 2.5-4 mg/day or 100µg/kg/day for children, of copper 0.5-1.5 mg/day or 20µg/kg/day for pediatric patients, of manganese 01.15-0.8mg/day or 2-10µg/kg/day for pediatric patients, of chromium 10-15µg/day or 01.14-0.20 µg/kg/day for pediatric patients, and of selenium 20-40µg/day or 3µg/kg/day (page 3). Americanregent.com teach Multitrace-5 has water content of 96.3-98.5% and zinc sulfate heptahydrate of 0.4-2.2% (Section 3.2). Americanregent.com further teach Multitrace-5 has a pH 1.5-3.5 (Section 9.1). Therefore, the instant claims are anticipated by the prior art.

Withdrawn and New Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the

claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Response to Applicant's Arguments

The rejection of claim 9 under 35 U.S.C. 103 as being unpatentable over Chang et al. (US Patent Application Publication 2015/0238527 A1, Published 08/27/2015) is moot since the claim is canceled.

The rejection of claims 1, 4, 5, 8, 10-12, 66, 70, 74 and 75 is/are rejected under 35 U.S.C. 103 as being unpatentable over Chang et al. (US Patent Application Publication 2015/0238527 A1, Published 08/27/2015) is withdrawn in view of the amendments to the claims.

The rejection of claims 1, 4-7, 10, 66, 70, 74 and 75 under 35 U.S.C. 103 as being unpatentable over Fahim (US Patent 4339438, Published 07/13/1982) is withdrawn in view of the amendments to the claims.

The rejection of claim 9 under 35 U.S.C. 103 as being unpatentable over Matsushita et al. (Japanese Patent Application 2000178181, Published 06/27/2000) is moot since the claim is cancelled.

The rejection of claims 1-10, 13, 16-19, 65-71, 74, and 75 under 35 U.S.C. 103 as being unpatentable over Matsushita et al. (Japanese Patent Application 2000178181, Published 06/27/2000) is withdrawn in view of the amendments to the claims.

The rejection of claims 14 and 15 under 35 U.S.C. 103 as being unpatentable over Chang et al. (US Patent Application Publication 2015/0238527 A1, Published 08/27/2015) as applied to claims 1, 4, 5, 8-12, 66, 70, 74 and 75 above, and further in view of Gray (US Patent 7077826 B1, Published 07/18/2006) is withdrawn in view of the amendments to the claims.

The rejection of claim 16 under 35 U.S.C. 103 as being unpatentable over Chang et al. (US Patent Application Publication 2015/0238527 A1, Published 08/27/2015) as applied to claims 1, 4, 5, 8-12, 66, 70, 74 and 75 above, and further in view of Laurie et al. (US Patent 7285292 B2, Published 10/23/2007) is withdrawn in view of the amendments to the claims.

This is a new ground of rejection of necessitated by the amendment to the claims.

Claim(s) 1-18, 65-71, and 74-75 is/are rejected under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019).

The claims are further directed to a composition comprising 3,000 or 1000 μg/mL zinc, 300 or 60 μg/mL copper, 60 or 6 μg/mL selenium, 55 or 3μg/mL, and 0 or 0.0001-0.25μg/mL of chromium.

The teachings of Drugs.com is disclosed above.

Drugs.com does not teach a preferred embodiment wherein the composition comprises 3,000 µg/mL zinc, 300 or 60 µg/mL copper, 60 or 6 µg/mL selenium, 55 or 3µg/mL, and 0 or 0.0001-0.25µg/mL of chromium. However, Drugs.com suggests such a composition.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the filing of the instant application adjust the amounts of the trace element constituents and arrive at the instantly claimed amount and have a reasonable expectation of success. One would have been motivated to do so through routine optimization in order to provide a concentration that would provide a preferred dosage based on the patient, their weight, and nutritional needs. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). For the foregoing reasons the instant claims are rendered obvious by the teachings of the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached M-F 9:30am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

EXHIBIT C

IN THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) An injectable composition comprising water[[,]] and about 4 µg to about 90 µg of selenium per 1 mL of the injectable composition[[,]] or about 4 µg to about 90 µg of selenium per 1 mL of the injectable composition and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition, wherein the injectable composition contains 0 µg per 1 mL to about 10 µg per 1 mL of iron, ~~and the injectable composition~~ does not contain any vitamins, and contains no chromium or chromium in an amount not to exceed 1 µg per 1 mL of the injectable composition and no aluminum or aluminum in an amount not to exceed 6 µg per 1 mL of the injectable composition.

2. (Original) The injectable composition of claim 1, wherein the injectable composition comprises 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition.

3. (Original) The injectable composition of claim 1, wherein the injectable composition comprises 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per 1 mL of injectable composition.

4. (Previously Presented) The injectable composition of claim 1, further comprising (i) iodine from about 0.0001 to about 0.2 mcg/kg/day, fluoride from about 0.0001 to about 2.7 mcg/kg/day, aluminum from about 0.0001 to about 0.6 mcg/kg/day or a mixture thereof; or (ii) iodine from about 0 to about 0.2 mcg/kg/day, fluoride from about 0 to about 2.7 mcg/kg/day, aluminum from about 0 to about 0.6 mcg/kg/day or a mixture thereof.

5. (Previously Presented) The injectable composition of claim 1, further comprising (i) iron from about 0.0001 to about 10 µg/mL, silicon from about 0.0001 to about 100 µg/mL, magnesium from about 0.0001 to about 50 µg/mL, calcium from about 0.0001 to about 50 µg/mL, boron

from about 0.0001 to about 50 µg/mL or a mixture thereof; (ii) silicon from about 0 to about 100 µg/mL, magnesium from about 0 to about 50 µg/mL, calcium from about 0 to about 50 µg/mL, boron from about 0 to about 50 µg/mL or a mixture thereof; or (iii) wherein the zinc is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection.

6. (Original) The injectable composition of claim 1, wherein the composition has a pH of about 1.0 to about 5.

7. (Original) The injectable composition of claim 6, wherein the composition further comprises a pH adjusting agent to adjust the pH.

8. (Original) The injectable composition of claim 1, wherein at least one of the zinc comprises about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises about 0.03 wt. percent to about 0.13 wt. percent, the manganese comprises about 0.0055 wt. percent to about 0.013 wt. percent, the selenium comprises about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 99.66 wt. percent based on a total weight of the injectable composition.

9. (Original) The injectable composition of claim 8, wherein at least one of the zinc comprises about 0.3 wt. percent, the copper comprises about 0.03 wt. percent, the manganese comprises about 0.0055 wt. percent, the selenium comprises about 0.006 wt. percent, or the water comprises from about 99.66 wt. percent based on a total weight of the injectable composition.

10. (Original) The injectable composition of claim 1, wherein the injectable composition is at least one of a preservative-free composition, a sterile composition, or a ready-to-use injectable aqueous composition.

11. (Original) The injectable composition of claim 1, wherein the injectable composition comprises a preservative.

12. (Original) The injectable composition of claim 11, wherein the preservative comprises benzyl alcohol in an amount of 0.9 % by weight based on a total weight of the injectable composition.

13. (Original) The injectable composition of claim 5, wherein the elemental zinc is from zinc sulfate or zinc sulfate heptahydrate, the elemental copper is from cupric sulfate or cupric sulfate pentahydrate, the elemental manganese is from manganese sulfate or manganese sulfate monohydrate and the elemental selenium is from selenious acid.

14. (Original) The injectable composition of claim 1, wherein the injectable composition is in a multi-dose vial.

15. (Original) The injectable composition of claim 14, wherein the multi-dose vial contains 10 mL of the injectable composition.

16. (Currently amended) The injectable composition of claim 1, wherein the injectable composition ~~has no chromium or~~ contains about 0.0001 µg/mL to about 0.25 µg/mL of chromium.

17. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition ~~has no aluminum or~~ contains about 1 ppm to about 6 µg/mL of aluminum.

18. (Original) The injectable composition of claim 1, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.3 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.015 to about 0.08 mg/day, and the selenium is selenious acid at a dose of about 20 to about 60 µg/day.

19. (Cancelled)

20.- 55. (Cancelled)

56. (Withdrawn) A method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

57.- 64. (Cancelled)

65. (Currently Amended) An injectable trace element composition comprising water, about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition, wherein the injectable composition contains 0 µg per 1 mL to about 10 µg per 1 mL of iron, ~~and the injectable composition~~ does not contain any vitamins, and contains no chromium or chromium in an amount not to exceed 1 µg per 1 mL of the injectable composition and no aluminum or aluminum in an amount not to exceed 6 µg per 1 mL of the injectable composition.

66. (Previously Presented) The injectable composition of claim 1, wherein zinc comprises from about 800 µg to about 4000 µg per 1mL of the injectable composition and the injectable composition is in a vial.

67. (Previously Presented) The injectable composition of claim 1, wherein copper comprises from about 40 µg to about 400 µg per 1mL of the injectable composition and the injectable composition is in a vial.

68. (Previously Presented) The injectable composition of claim 1, wherein selenium comprises from about 4 µg to about 90 µg per 1mL of the injectable composition and the injectable composition is in a vial.

69. (Previously Presented) The injectable composition of claim 1, wherein manganese comprises from about 1 µg to about 80 µg per 1mL of the injectable composition and the injectable composition is in a vial.

70. (Original) The injectable composition of claim 1, wherein the zinc, copper, selenium, manganese are in elemental or salt form.

71. (Original) The injectable composition of claim 7, wherein the pH adjusting agent is at least sodium hydroxide or sulfuric acid.

72. (Cancelled)

73. (Cancelled)

74. (Original) The injectable composition of claim 1, wherein the injectable composition contains less than about 0.25 µg/mL of chromium.

75. (Previously Presented) The injectable composition of claim 1, wherein permitted daily limits (PDL) of the injectable composition do not exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of

calcium, about 10 µg/ day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

76. (Currently Amended) The injectable composition of claim [[2]] 1, wherein the injectable composition ~~has no chromium or~~ contains ~~about 0.0001 µg/mL to about 0.25 µg/mL of~~ chromium in an amount not to exceed 1 µg per 1 mL of the injectable composition and the injectable composition contains ~~no aluminum or~~ aluminum in an amount not to exceed ~~contains about 1 ppm to about 6 µg/mL of aluminum~~ 6 µg per 1 mL of the injectable composition.

77. (New) The injectable composition of claim 65, wherein the injectable composition contains no chromium and the injectable composition contains no aluminum.

EXHIBIT D

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/365,695	07/01/2021	Gopal Anyarambhatla	1848-32 US	8197

109802 7590 10/26/2022

Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

EXAMINER	
SOROUSH, ALI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
10/26/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

npinou@slsllp.com
smoon@slsllp.com
wschmidt@slsllp.com

Office Action Summary	Application No. 17/365,695	Applicant(s) Anyarambhatla et al.	
	Examiner ALI SOROUSH	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 05/25/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-18,56,65-71 and 74-77 is/are pending in the application.

5a) Of the above claim(s) 56 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-18,65-71 and 74-77 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 10022022.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/07/2022 has been entered.

Claim Status

Claims 1-18, 56, 65-71, and 74-77 are pending.

Claims 19, 55 and 57-64 were previously cancelled and claim 72 is cancelled.

Claim 56 is withdrawn as being directed to a non-elected invention.

Claim 77 is newly added.

Claim 1, 16, 17, 65 and 76 are currently amended.

Claims 1-18, 65-71, and 74-77 have been examined.

Claims 1-18, 65-71, and 74-77 are rejected.

Priority

Priority to application 63/047708 filed on 07/02/2020 is acknowledged.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/07/2022 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Withdrawn Claim Rejections - 35 USC § 102

Response to Applicant's Arguments

The rejection of claims 1, 4-8, 10-15, 17, 18, 65-71, and 75 under 35 U.S.C. 102(a)(1) as being anticipated by Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019) is withdrawn in view of the amendment to the claims.

Maintained and New Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the

claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

This rejection is maintained and modified in view of the amendments to the claims.

Claim(s) 1-18, 65-71, and 74-77 is/are rejected under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019).

The claims are directed to an injectable aqueous composition comprising water, 800-4,000µg/ml of zinc, preferably elemental zinc, more preferably zinc sulfate heptahydrate, 40-400µg/ml copper, preferably elemental copper, more preferably cupric sulfate, 1-80µg/ml manganese, preferably elemental manganese, more preferably manganese sulfate, and 4-90µg/ml selenium, more preferably

elemental selenium, and most preferably selenious acid; wherein the composition is a sterile composition. The claims are further directed to the composition has a pH of about 1.0-5. The claims further comprise a pH adjusting agent such as sodium hydroxide and/or sulfuric acid. The claims are further directed to the composition comprising a preservative. The claims are further directed to the composition comprising as the preservative benzoyl alcohol in an amount of 0.9% based on the total weight of the composition. The composition further comprises iodine from about 0-0.2 mcg/kg/day, fluoride from about 0-2.7, aluminum from about 0-0.6 mcg/kg/day or a mixture thereof. The composition further comprises iron from about 0-10 µg/ml, silicon from about 0-100 µg/ml, magnesium from about 0-50 µg/ml, calcium from about 0-50µg/ml, boron from about 0-50µg or mixtures thereof. The claims are further directed to the composition wherein the permitted daily limits (PDL) of the injectable composition do not exceed for example about 0.4µg/day of cadmium. The claims are further directed to the composition being in a multi-dose vial comprising 10mL of the composition. The claims are further directed to a composition comprising 3,000 or 1000 µg/mL zinc, 300 or 60 µg/mL copper, 60 or 6 µg/mL selenium, 55 or 3µg/mL manganese, and 0 or 0.0001-0.25µg/mL of chromium.

Drugs.com teach Multitrace-5 is a sterile nonpyrogenic solution trace element injection for total parenteral nutrition (Page 1, Multitrace-5 Description). Each mL comprises 1000µg zinc, 400µg copper, 100µg manganese, 4µg chromium, 20µg selenium, 0.9% benzyl alcohol preservative, sulfuric acid and/or sodium hydroxide for pH adjustment, and water for injection in 10mL multiple dose vial (Page 3, Container). The ingredients are zinc sulfate heptahydrate, cupric sulfate, manganese sulfate, chromic chloride, selenious acid, benzoyl alcohol, sulfuric acid, sodium hydroxide, and water (page 4, Ingredient Name). The suggested dosage level of zinc is 2.5-4 mg/day or 100µg/kg/day for children, of copper 0.5-1.5 mg/day or 20µg/kg/day for pediatric patients, of manganese 01.15-0.8mg/day or 2-10µg/kg/day for pediatric patients, of chromium 10-15µg/day or 01.14-0.20 µg/kg/day for pediatric patients, and of selenium 20-40µg/day or 3µg/kg/day (page 3). Americanregent.com teach Multitrace-5 has water

content of 96.3-98.5% and zinc sulfate heptahydrate of 0.4-2.2% (Section 3.2). Americanregent.com further teach Multitrace-5 has a pH 1.5-3.5 (Section 9.1).

Drugs.com does not teach a preferred embodiment wherein the composition comprises 3,000 µg/mL zinc, 300 or 60 µg/mL copper, 60 or 6 µg/mL selenium, and 55 or 3µg/mL manganese, and 0 or 0.0001-0.25µg/mL of chromium. However, Drugs.com suggests such a composition.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the filing of the instant application adjust the amounts of the trace element constituents and arrive at the instantly claimed amount and have a reasonable expectation of success. One would have been motivated to do so through routine optimization in order to provide a concentration that would provide a preferred dosage based on the patient, their weight, and nutritional needs. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). For the foregoing reasons the instant claims are rendered obvious by the teachings of the prior art.

Response to Applicant's Arguments

Applicant argues that it would not have been obvious to one of ordinary skill in the art to modify the Multitrace-5 composition to eliminate or reduce to trace amounts chromium in the composition. Applicant's argument has been fully considered but found not to be persuasive. One of ordinary skill in the art would be motivated to adjust or eliminate the amount of chromium based on the nutritional needs of a patient being administered a parenteral composition comprising a mixture of elemental compounds. For example, a patient that has no deficiency and/or supplemental need of chromium could be given a composition which is free of chromium.

Applicant also argues that if one adjusted the amount of chromium in the Multitrace-5 composition then all the other elements remaining the composition would be outside the instantly claimed range. Applicant's argument has been fully considered but found not to be persuasive. It appears Applicant's arguments premise is based on the assertion that one would adjust the amounts of the elements by diluting the composition of Multitrace-5. However, one of ordinary skill in the art would be equally motivated to formulate a composition comprising the instantly claimed elements in the instantly claimed amounts not by diluting Multitrace-5 looking to Multitrace-5 as blueprint to form a new composition but adjust for the nutritional needs of the patient to be treated. That is if one of ordinary skill in the art has a patient needing nutritional supplementation of zinc, copper, selenium, and manganese but not chromium, aluminum, iron, and/or vitamins, one of ordinary skill in art would be able to make such a composition.

It should be noted that the composition of Drugs.com does not include any aluminum.

This is a new ground of rejection necessitated by the amendments to the claims.

Claim(s) 1-18, 65-71, and 74-77 is/are rejected under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019) in view of Burjonrappa et al. (Role of trace elements in parenteral nutrition support of the surgical neonate, Published 2012).

The claims are directed to an injectable aqueous composition comprising water, 800-4,000µg/ml of zinc, preferably elemental zinc, more preferably zinc sulfate heptahydrate, 40-400µg/ml copper, preferably elemental copper, more preferably cupric sulfate, 1-80µg/ml manganese, preferably elemental manganese, more preferably manganese sulfate, and 4-90µg/ml selenium, more preferably

elemental selenium, and most preferably selenious acid; wherein the composition is a sterile composition. The claims are further directed to the composition has a pH of about 1.0-5. The claims further comprise a pH adjusting agent such as sodium hydroxide and/or sulfuric acid. The claims are further directed to the composition comprising a preservative. The claims are further directed to the composition comprising as the preservative benzoyl alcohol in an amount of 0.9% based on the total weight of the composition. The composition further comprises iodine from about 0-0.2 mcg/kg/day, fluoride from about 0-2.7, aluminum from about 0-0.6 mcg/kg/day or a mixture thereof. The composition further comprises iron from about 0-10 µg/ml, silicon from about 0-100 µg/ml, magnesium from about 0-50 µg/ml, calcium from about 0-50µg/ml, boron from about 0-50µg or mixtures thereof. The claims are further directed to the composition wherein the permitted daily limits (PDL) of the injectable composition do not exceed for example about 0.4µg/day of cadmium. The claims are further directed to the composition being in a multi-dose vial comprising 10mL of the composition. The claims are further directed to a composition comprising 3,000 or 1000 µg/mL zinc, 300 or 60 µg/mL copper, 60 or 6 µg/mL selenium, 55 or 3µg/mL manganese, and 0 or 0.0001-0.25µg/mL of chromium.

Drugs.com teach Multitrace-5 is a sterile nonpyrogenic solution trace element injection for total parenteral nutrition (Page 1, Multitrace-5 Description). Each mL comprises 1000µg zinc, 400µg copper, 100µg manganese, 4µg chromium, 20µg selenium, 0.9% benzyl alcohol preservative, sulfuric acid and/or sodium hydroxide for pH adjustment, and water for injection in 10mL multiple dose vial (Page 3, Container). The ingredients are zinc sulfate heptahydrate, cupric sulfate, manganese sulfate, chromic chloride, selenious acid, benzoyl alcohol, sulfuric acid, sodium hydroxide, and water (page 4, Ingredient Name). The suggested dosage level of zinc is 2.5-4 mg/day or 100µg/kg/day for children, of copper 0.5-1.5 mg/day or 20µg/kg/day for pediatric patients, of manganese 01.15-0.8mg/day or 2-10µg/kg/day for pediatric patients, of chromium 10-15µg/day or 01.14-0.20 µg/kg/day for pediatric patients, and of selenium 20-40µg/day or 3µg/kg/day (page 3). Americanregent.com teach Multitrace-5 has water

content of 96.3-98.5% and zinc sulfate heptahydrate of 0.4-2.2% (Section 3.2). Americanregent.com further teach Multitrace-5 has a pH 1.5-3.5 (Section 9.1).

Drugs.com does not teach a preferred embodiment wherein the composition comprises 3,000 µg/mL zinc, 300 or 60 µg/mL copper, 60 or 6 µg/mL selenium, and 55 or 3µg/mL manganese, and 0 or 0.0001-0.25µg/mL of chromium. However, Drugs.com suggests such a composition.

Burjonrappa et al. teach "Surprisingly, preterm infants receiving parenteral Cr exhibited poorer glucose tolerance, leading some experts to question its metabolic role in the neonatal population and the actual need for supplementation in neonates … Chromium may also be associated with TPN-related nephropathy, with Cr supplementation for as little as 3 weeks causing reductions in glomerular filtration rate and elevations in serum creatinine … This has led some experts to recommend a reduction in Cr supplementation in parenteral formulas to avoid toxicity … Chromium supplementation should be discontinued in infants with renal insufficiency" (page 767, section 2.4.3). "In certain settings, it may be more appropriate to individualize trace element supplementation based on the predetermined physiologic need rather than using bundled packages of trace elements as is the current norm" (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the filing of the instant application adjust the amounts of the trace element constituents and arrive at the instantly claimed amount and have a reasonable expectation of success. One would have been motivated to do so through routine optimization in order to provide a concentration that would provide a preferred dosage based on the patient, their weight, and nutritional needs. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA

1955). In particular one of ordinary skill in the art wanting to provide trace element supplementation to preterm infants or to avoid the possibility of nephropathy would formulate the composition with little or no chromium. Furthermore, one of ordinary skill in the art would be motivated to adjust the amounts of the trace elements in the composition of Drugs.com not by simply diluting the composition with water but to the amounts needed by a particular patient in order to give an individualized trace element formulation. For the foregoing reasons the instant claims are rendered obvious by the teachings of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached M-F 9:30am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional

questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

EXHIBIT E

IN THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) An injectable composition comprising water, ~~and about 4 µg to about 90 µg of selenium per 1 mL of the injectable composition or~~ about ~~4 µg to about~~ [[90]] 60 µg of selenium, ~~per 1 mL of the injectable composition and at least one of~~ about ~~800 µg to about~~ [[4,000]] 3,000 µg of zinc, about ~~40 µg to about~~ [[400]] 300 µg of copper, [[or]] and about ~~1 µg to about~~ [[80]] 55 µg of manganese per 1 mL of the injectable composition, wherein the injectable composition contains 0 µg per 1 mL to about 10 µg per 1 mL of iron, does not contain any vitamins, ~~and~~ contains no added chromium ~~or chromium in an amount not to exceed 1 µg per 1 mL of the injectable composition~~ and no aluminum or aluminum in an amount not to exceed 6 µg per 1 mL of the injectable composition.

2. (Original) The injectable composition of claim 1, wherein the injectable composition comprises 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition.

3. (Currently Amended) The injectable composition of claim [[1]] 81, wherein the injectable composition comprises 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per 1 mL of injectable composition.

4. (Currently Amended) The injectable composition of claim [[1]] 78, wherein the injectable composition comprises 3,000 µg of zinc, 300 µg of copper, 60 µg of selenium, and 55 µg of manganese per 1 mL of the injectable composition ~~further comprising (i) iodine from about 0.0001 to about 0.2 mcg/kg/day, fluoride from about 0.0001 to about 2.7 mcg/kg/day, aluminum from about 0.0001 to about 0.6 mcg/kg/day or a mixture thereof; or (ii) iodine from about 0 to about 0.2 mcg/kg/day, fluoride from about 0 to about 2.7 mcg/kg/day, aluminum from about 0 to about 0.6 mcg/kg/day or a mixture thereof~~.

5. (Currently Amended) The injectable composition of claim 1, further comprising (i) ~~iron from about 0.0001 to about 10 µg/mL,~~ silicon from about 0.0001 to about 100 µg/mL, magnesium from about 0.0001 to about 50 µg/mL, calcium from about 0.0001 to about 50 µg/mL, boron from about 0.0001 to about 50 µg/mL or a mixture thereof; (ii) silicon from about 0 to about 100 µg/mL, magnesium from about 0 to about 50 µg/mL, calcium from about 0 to about 50 µg/mL, boron from about 0 to about 50 µg/mL or a mixture thereof; or (iii) wherein the zinc is elemental zinc, the copper is elemental copper, the selenium is elemental selenium, the manganese is elemental manganese and the water is sterile water for injection.

6. (Currently Amended) The injectable composition of claim 1, wherein the composition has a pH of about 1.0 to about 5 and the injectable composition is for use in adult or pediatric human patients.

7. (Original) The injectable composition of claim 6, wherein the composition further comprises a pH adjusting agent to adjust the pH.

8. (Currently Amended) The injectable composition of claim [[1]] 78, wherein the zinc is elemental zinc from zinc sulfate or zinc sulfate heptahydrate, the copper is elemental copper from cupric sulfate or cupric sulfate pentahydrate, the manganese is elemental manganese from manganese sulfate or manganese sulfate monohydrate and the selenium is elemental selenium from selenious acid ~~at least one of the zinc comprises about 0.23 wt. percent to about 1.33 wt. percent, the copper comprises about 0.03 wt. percent to about 0.13 wt. percent, the manganese comprises about 0.0055 wt. percent to about 0.013 wt. percent, the selenium comprises about 0.002 wt. percent to about 0.02 wt. percent, or the water comprises from about 96 wt. percent to about 99.66 wt. percent based on a total weight of the injectable composition~~.

9. (Currently Amended) The injectable composition of claim [[8]] 81, wherein the zinc is elemental zinc from zinc sulfate or zinc sulfate heptahydrate, the copper is elemental copper from cupric sulfate or cupric sulfate pentahydrate, the manganese is elemental manganese from manganese sulfate or manganese sulfate monohydrate and the selenium is elemental selenium

from selenious acid ~~at least one of the zinc comprises about 0.3 wt. percent, the copper comprises about 0.03 wt. percent, the manganese comprises about 0.0055 wt. percent, the selenium comprises about 0.006 wt. percent, or the water comprises from about 99.66 wt. percent based on a total weight of the injectable composition~~.

10. (Original) The injectable composition of claim 1, wherein the injectable composition is at least one of a preservative-free composition, a sterile composition, or a ready-to-use injectable aqueous composition.

11. (Original) The injectable composition of claim 1, wherein the injectable composition comprises a preservative.

12. (Original) The injectable composition of claim 11, wherein the preservative comprises benzyl alcohol in an amount of 0.9 % by weight based on a total weight of the injectable composition.

13. (Currently Amended) The injectable composition of claim [[5]] 2, wherein the zinc is elemental zinc [[is]] from zinc sulfate or zinc sulfate heptahydrate, the copper is elemental copper [[is]] from cupric sulfate or cupric sulfate pentahydrate, the manganese is elemental manganese [[is]] from manganese sulfate or manganese sulfate monohydrate and the selenium is elemental selenium [[is]] from selenious acid.

14. (Original) The injectable composition of claim 1, wherein the injectable composition is in a multi-dose vial.

15. (Original) The injectable composition of claim 14, wherein the multi-dose vial contains 10 mL of the injectable composition.

16. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains about 0.0001 µg/mL to about 0.25 µg/mL of chromium as an impurity.

17. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains about 1 ppm to about 6 µg/mL of aluminum as an impurity.

18. (Original) The injectable composition of claim 1, wherein the zinc is zinc sulfate heptahydrate at a dose of about 2.5 to about 7 mg/day, the copper is cupric sulfate pentahydrate at a dose of about 0.3 to about 1.5 mg/day, the manganese is manganese sulfate monohydrate at a dose of about 0.015 to about 0.08 mg/day, and the selenium is selenious acid at a dose of about 20 to about 60 µg/day.

19. (Cancelled)

20.- 55. (Cancelled)

56. (Withdrawn) A method of maintaining plasma trace elements in a patient in need thereof, the method comprising administering at least an injectable composition to the patient, the injectable composition comprising water, and at least one of about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, or about 1 µg to about 80 µg of manganese per 1 mL of the injectable composition.

57.- 64. (Cancelled)

65. (Currently Amended) An injectable trace element composition comprising water, and as the active ingredients about 7.41 mg of zinc sulfate or zinc sulfate heptahydrate, about 0.75 mg of cupric sulfate or cupric sulfate pentahydrate, about 151 mcg of manganese sulfate or manganese sulfate monohydrate and about 98 mcg of selenious acid ~~about 800 µg to about 4,000 µg of zinc, about 40 µg to about 400 µg of copper, about 4 µg to about 90 µg of selenium, and about 1 µg to about 80 µg of manganese~~ per 1 mL of the injectable composition, wherein the injectable composition contains impurities of chromium, aluminum, and iron, wherein the impurities are chromium in an amount not to exceed 1 µg, aluminum in an amount not to exceed 6 µg, and 0 µg

to about 10 µg of the iron ~~the injectable composition contains 0 µg per 1 mL to about 10 µg per 1 mL of iron does not contain any vitamins, and contains no chromium or chromium in an amount not to exceed 1 µg per 1 mL of the injectable composition and no aluminum or aluminum in an amount not to exceed 6 µg~~ per 1 mL of the injectable composition.

66. (Currently Amended) The injectable composition of claim 1, wherein ~~zinc comprises from about 800 µg to about 4000 µg per 1mL of the injectable composition and~~ the injectable composition is in a vial.

67. (Currently Amended) The injectable composition of claim 81 [[1]], wherein ~~copper comprises from about 40 µg to about 400 µg per 1mL of the injectable composition and~~ the injectable composition is in a vial.

68. (Cancelled)

69. (Cancelled)

70. (Original) The injectable composition of claim 1, wherein the zinc, copper, selenium, manganese are in elemental or salt form.

71. (Original) The injectable composition of claim 7, wherein the pH adjusting agent is at least sodium hydroxide or sulfuric acid.

72. (Cancelled)

73. (Cancelled)

74. (Currently Amended) The injectable composition of claim 1, wherein the injectable composition contains less than about 0.25 µg/mL of chromium as an impurity.

75. (Previously Presented) The injectable composition of claim 1, wherein permitted daily limits (PDL) of the injectable composition do not exceed about 0.4 µg/ day of cadmium, about 0.5 µg/ day of lead, about 1.5 µg/ day of arsenic, about 0.4 µg/ day of mercury, about 1 µg/ day of cobalt, about 2 µg/ day of vanadium, about 4 µg/ day of nickel, about 1.6 µg/ day of thallium, about 20 µg/ day of gold, about 2 µg/ day of palladium, about 2 µg/ day of iridium, about 2 µg/ day of osmium, about 2 µg/ day of rhodium, about 2 µg/ day of ruthenium, about 2 µg/ day of silver, about 2 µg/ day of platinum, about 50 µg/ day of lithium, about 18 µg/ day of antimony, about 140 µg/ day of barium, about 300 µg/ day of molybdenum, about 120 µg/ day of tin, about 1 µg/ day of chromium, about 6 µg/ day of aluminum, about 50 µg/ day of boron, about 50 µg/ day of calcium, about 10 µg/ day of iron, about 94,000 µg/ day of potassium, about 50 µg/ day of magnesium, about 24,000 µg/ day of sodium, about 1 µg/ day of tungsten, and/or about 100 µg/ day of silicon.

76. (Previously Presented) The injectable composition of claim 1, wherein the injectable composition contains chromium in an amount not to exceed 1 µg per 1 mL of the injectable composition and the injectable composition contains aluminum in an amount not to exceed 6 µg per 1 mL of the injectable composition.

77. (Previously Presented) The injectable composition of claim 65, wherein the injectable composition contains no chromium and the injectable composition contains no aluminum.

78. (New) An injectable composition comprising water, active ingredients comprising about 60 µg of selenium, about 3,000 µg of zinc, about 300 µg of copper, and about 55 µg of manganese per 1 mL of the injectable composition, and impurities of chromium, aluminum, and iron, wherein the impurities are chromium in an amount not to exceed 1 µg, aluminum in an amount not to exceed 6 µg, and 0 µg to about 10 µg of the iron per 1 mL of the injectable composition.

79. (New) An injectable composition comprising water, and active ingredients, the active ingredients consisting of about 60 µg of selenium, about 3,000 µg of zinc, about 300 µg of copper, and about 55 µg of manganese per 1 mL of the injectable composition.

80. (New) The injectable composition of claim 79, wherein the active ingredients consists of 60 µg of selenium, 3,000 µg of zinc, 300 µg of copper, and 55 µg of manganese per 1 mL of the injectable composition.

81. (New) An injectable composition comprising water, about 6 µg of selenium, about 1,000 µg of zinc, about 60 µg of copper, and about 3 µg of manganese per 1 mL of the injectable composition, wherein the injectable composition contains 0 µg per 1 mL to about 10 µg per 1 mL of iron, does not contain any vitamins, contains no added chromium and no aluminum or aluminum in an amount not to exceed 6 µg per 1 mL of the injectable composition.

82. (New) An injectable composition comprising water, active ingredients comprising about 6 µg of selenium, about 1,000 µg of zinc, about 60 µg of copper, and about 3 µg of manganese per 1 mL of the injectable composition, and impurities of chromium, aluminum, and iron, wherein the impurities are chromium in an amount not to exceed 1 µg, aluminum in an amount not to exceed 6 µg, and 0 µg to about 10 µg of the iron per 1 mL of the injectable composition.

83. (New) The injectable composition of claim 82, wherein the injectable composition comprises 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese per 1 mL of injectable composition.

84. (New) An injectable composition comprising water, and active ingredients, the active ingredients consisting of about 6 µg of selenium, about 1,000 µg of zinc, about 60 µg of copper, and about 3 µg of manganese per 1 mL of the injectable composition.

85. (New) The injectable composition of claim 84, wherein the active ingredients consist of 6 µg of selenium, 1,000 µg of zinc, 60 µg of copper, and 3 µg of manganese per 1 mL of the injectable composition.

86. (New) An injectable composition comprising water, and active ingredients, the active ingredients consisting of about 2,470 mcg of zinc sulfate or zinc sulfate heptahydrate, about 150 mcg of cupric sulfate or cupric sulfate pentahydrate, about 8.22 mcg of manganese sulfate or manganese sulfate monohydrate and about 9.8 mcg of selenious acid per 1 mL of the injectable composition.

87. (New) The injectable composition of claim 86, wherein the active ingredients consist of 2,470 mcg of zinc sulfate or zinc sulfate heptahydrate, 150 mcg of cupric sulfate or cupric sulfate pentahydrate, 8.22 mcg of manganese sulfate or manganese sulfate monohydrate and 9.8 mcg of selenious acid per 1 mL of the injectable composition.

88. (New) The injectable composition of claim 86, wherein the injectable composition comprises sodium hydroxide or sulfuric acid as a pH adjusting agent.

89. (New) An injectable composition comprising water, and active ingredients, the active ingredients consisting of about 7.41 mg of zinc sulfate or zinc sulfate heptahydrate, about 0.75 mg of cupric sulfate or cupric sulfate pentahydrate, about 151 mcg of manganese sulfate or manganese sulfate monohydrate and about 98 mcg of selenious acid per 1 mL of the injectable composition.

90. (New) The injectable composition of claim 89, wherein the active ingredients consist of 7.41 mg of zinc sulfate or zinc sulfate heptahydrate, 0.75 mg of cupric sulfate or cupric sulfate pentahydrate, 151 mcg of manganese sulfate or manganese sulfate monohydrate and 98 mcg of selenious acid per 1 mL of the injectable composition.

91. (New) The injectable composition of claim 89, wherein the injectable composition comprises sodium hydroxide or sulfuric acid as a pH adjusting agent.

92. (New) The injectable composition of claim 1, wherein the chromium is elemental chromium from chromium chloride.

93. (New) The injectable composition of claim 81, wherein the chromium is elemental chromium from chromium chloride.

94. (New) The injectable composition of claim 81, wherein the injectable composition is for use in pediatric or neonatal human patients.

95. (New) The injectable composition of claim 1, wherein the injectable composition is for use in adult or pediatric human patients.

96. (New) The injectable composition of claim 70, wherein the ratio of elemental copper to elemental zinc is 1:10.

97. (New) The injectable composition of claim 81, wherein the zinc is elemental zinc, the copper is elemental copper, the manganese is elemental manganese and the selenium is elemental selenium.

98. (New) The injectable composition of claim 97, wherein the ratio of elemental selenium to elemental copper is 1:10.

99. (New) The injectable composition of claim 6, wherein the injectable composition comprises a silicon impurity.

100. (New) The injectable composition of claim 6, wherein the injectable composition is in a glass vial or ampule and has a silicon impurity in an amount of not more than 100 µg/mL.

101. (New) The injectable composition of claim 1, wherein the injectable composition is stable for up to two years.

102. (New) The injectable composition of claim 81, wherein the injectable composition is stable for up to two years.

103. (New) The injectable composition of claim 1, wherein the injectable composition has a bacterial endotoxin limit of not more than 50 EU/mL.

104. (New) The injectable composition of claim 81, wherein the injectable composition has a bacterial endotoxin limit of less than 17.50 EU/mL.

EXHIBIT F

REMARKS

By this response, claims 1 and 4 have been amended and new claims 78-80, 95 and 96 have been added to include the features of claim 2 that the injectable composition contains as active ingredients a combination of trace elements of about 3,000 µg of zinc, about 300 µg of copper, about 60 µg of selenium and about 55 µg of manganese per 1 mL of the injectable composition, no added chromium or chromium as an impurity and no aluminum or contaminant amounts of aluminum in the injectable composition. These claims include the unique formulation (e.g., now known as Tralement®) that can be used, for example, in adult and pediatric patients. The ratio of elemental copper to elemental zinc here is 1:10. Support for the amendments to claims 1 and 4 and new claims 78-80, 95 and 96 can be found in original claims 1, 2, 16-17, 63, paragraphs [061]-[063], [074], [093]-[094], [0108], [0118], [0130], [0136], [0140]-[0141], [0158], [0173]-[0174], [0195]-[0196], [0211], [0213]-[0214], [0271], [0275], [0293], [0300], Examples 1, 11, Tables 1, 2, 4, 8, 30, 34, and 35 of the specification.

Claim 3 has been amended and new claims 81, 82, 83, 94, 97 and 98 have been added to include that the injectable composition contains as active ingredients a combination of trace elements of about 1,000 µg of zinc, about 60 µg of copper, about 6 µg of selenium and about 3 µg of manganese per 1 mL of the injectable composition and that the injectable composition has no added chromium or chromium as an impurity and no aluminum or contaminant amounts of aluminum in the injectable composition. These claims include the unique formulation (e.g., now known as Multrys®) that can be used, for example, in pediatric and neonatal patients. The ratio of elemental selenium to elemental copper here is 1:10. Support for the amendments to claim 3 and new claims 81, 82, 83, 94, 97 and 98 can be found in original claims 1, 2, 3, 16-17, 63, paragraphs [061]-[064], [074], [093]-[094], [0108], [0118], [0130], [0136], [0139]-[0140], [0159], [0173]-[0174], [0195]-[0196], [0211], [0213]-[0214], [0271], [0276], [0293], [0300], Example 12, Tables 2, 4, 8, 30, 34, and 35 of the specification.

Claim 4 has been amended to specifically recite the active ingredients of claim 78. Claim 5 has been amended to make it consistent with amended claim 1. Claims 8, 9 and 65 have been amended to include the specific mineral salts or acid of the elemental active ingredients. Support for this amendment can be found, for example, in original claims 13, 18, 19, paragraphs [065]-[070], [086], [091], [0134], [0284], Examples 11, 12, Tables 1, 5 and 6 of the specification.

Claim 13 has been amended to make it consistent with claim 2. Claims 16, 17 and 74 have been amended to include that the chromium and/or aluminum is an impurity. Support for this amendment can be found, for example, in paragraphs [097], [0118], [0173]-[0174], [0209], [0300], Tables 30 and 33 of the specification.

Claim 66 has been amended to depend on claim 1 and claim 67 has been amended to depend on claim 81.

New claims 79 and 80, and 89-91 have been added and include that the injectable composition contains active ingredients that "consist of" about 3,000 µg of zinc, about 300 µg of copper, about 60 µg of selenium and about 55 µg of manganese per 1 mL of the injectable composition or the specific mineral salts or acid of the elemental active ingredients. These claims include the unique formulation (e.g., now known as Tralement®) that can be used in, for example, adult and pediatric patients. Therefore, these claims exclude other active ingredients from being added. Support for new claims 79 and 80, 89-91 can be found, for example, in original claims 1, 2, 13, 18, 19, paragraphs [022]-[023], [060]-[063], [065]-[069], [086], [091], [0106], [0108], [0134], [0154], [0156], Examples 1, 11, 12, Tables 1, 6, 8, 11, 26, 34 and 35 of the specification.

New claims 84-88 have been added and include that the injectable composition contains active ingredients that "consist of" about 1,000 µg of zinc, about 60 µg of copper, about 6 µg of selenium and about 3 µg of manganese per 1 mL of the injectable composition or the specific mineral salts or acid of the elemental active ingredients. These claims include the unique formulation (e.g., now known as Multrys®) that can be used in, for example, pediatric and adult patients. Therefore, these claims exclude other active ingredients from being added. Support for new claims 84-88 can be found, for example, in original claims 1, 2, 3, 13, 18, 19, paragraphs [024], [060]-[061], [065], [091], [0106], [0108], [0134], [0156], Examples 12, Tables 8, 30 and 35 of the specification.

New claims 92 and 93 have been added and include that the impurity is elemental chromium from chromium chloride. Support for new claims 92 and 93 can be found, for example, in original claims 1, 2, 3, 16, 17, 52, paragraphs [0139], [0140] and [0300].

New claims 99 and 100 have been added and include that the impurity is silicon or silicon in an amount of not more than 100 µg/mL. Support for new claims 99 and 100 can be found, for example, in original claim 5, claims 30-32, and Tables 2 and 30.

New claims 101 and 102 have been added and include that the injectable composition has a stability of up to 2 years. Support for new claims 101 and 102 can be found, for example, in paragraphs [0130], [0143], [0267] and Table 31.

New claims 103 and 104 have been added and include that the injectable composition has a bacterial endotoxin limit of 50 EU/mL or a bacterial endotoxin limit of less than 17.50 EU/mL, respectively. Support for new claims 103 and 104 can be found, for example, in Tables 2 and 30.

Claims 68-69 have been cancelled without disclaimer. Any rejections concerning claims 68-69 are thus moot. Applicant reserves the right to pursue cancelled claims 68-69 in one or more continuing applications. The amendments do not add new matter. Applicant respectfully requests entry of these amendments and allowance of the pending claims.

1. Interview Summary

In responding to the October 26, 2022 Office Action (Office Action), Applicant's representative, William D. Schmidt, conducted a telephone interview with Examiner Ali Soroush on January 19, 2023. Applicant thanks the Examiner for the time generously extended during the interview, in which Applicant discussed proposed amendments to the claims of the current application. Specifically, the 35 U.S.C. §103 rejection was discussed and that the proposed claims are directed to unique multiple trace element products. The Multitrace® 5 references cited in the Office Action have chromium as one of its active ingredients in contrast to the proposed claims that include no chromium or contaminant amounts of chromium that are not an active ingredient. Moreover, the Multitrace® 5 references cited would not be used as a "blue print" to design unique multiple trace element products as recited in the claims. This is especially so as the cited Burjonrappa reference, which promotes using a single trace element rather than a combination trace element product is incompatible with the Multitrace® 5 references and a person of ordinary skill in the art would not combine them together the way the Office does. Applicant also discussed that the Office considers the claims as "a new composition". However, the Office considers this new composition to be allegedly obvious as a result of routine optimization. Applicant respectfully disagreed with the Office and there was a discussion of providing declarations of non-obviousness including secondary considerations. An agreement

was not reached. Applicant has amended the claims and provides declarations of non-obviousness consistent with the interview.

2. Claim Rejections Under 35 U.S.C. §103

The Office rejected: (i) claims 1, 4-8, 10-15, 17-18, 65-71, and 75 under 35 U.S.C. §103 as allegedly being obvious in view of Drugs.com (Multitrace® 5, Published September 7, 2015) as evidenced by Americanregent.com (Multitrace® 5 Concentrate (Trace Elements Injection 5, USP), and Multitrace® 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published January 9, 2019) (collectively the Multitrace® 5 references); and (ii) claims 1-18, 65-71, and 74-77 under 35 U.S.C. §103 as allegedly being obvious in view of the Multitrace® 5 references in combination with "Role of trace elements in parenteral nutrition support of the surgical neonate," Journal of Pediatric Surgery 47, 760-771 (April 2012) (Burjonrappa). Applicant respectfully disagrees with the Office.

Regarding item (i) above, and to advance the application without agreeing to the merits of this aspect of the rejection, Applicant has amended the claims to include the features of claims 2 or 3. Because claims 2 or 3 are not part of item (i) of the rejection, this aspect of the rejection is moot.

A. Multitrace® 5, Multitrace® 5 Concentrate Do Not Make the Current Claims Obvious

As to item (ii) above, Applicant respectfully traverses this aspect of the rejection. As an initial matter, among other things, claims 1 and 4 have been amended and new claims 78-80 and 95 have been added to include the features of claim 2 that the injectable composition contains a combination of trace elements of about 3,000 µg of zinc, about 300 µg of copper, about 60 µg of selenium and about 55 µg of manganese per 1 mL of the injectable composition and that the injectable composition has no added chromium or chromium as an impurity and no aluminum or contaminant amounts of aluminum. These claims include the unique formulation (e.g., now known as Tralement®) that can be used, for example, in adult and pediatric patients.

Also, claim 3 has been amended and new claims 81, 82 and 83 have been added to include that the injectable composition contains as active ingredients a combination of trace elements of about 1,000 µg of zinc, about 60 µg of copper, about 6 µg of selenium and about 3 µg of manganese per 1 mL of the injectable composition and that the injectable composition has no

added chromium or chromium as an impurity and no aluminum or contaminant amounts of aluminum. These claims include the unique formulation (e.g., known now as Multrys®) that can be used, for example, in pediatric and neonatal patients.

Of note, Applicant directs the Office's attention to new claims 79-80, 84-88 and 89-91 that have been added and include that the injectable composition contains active ingredients that "consist of" zinc, copper, selenium and manganese per 1 mL of the injectable composition or the specific mineral salts or acid of the elemental active ingredients. These claims include the unique formulation but exclude other active ingredients from being added.

As explained in detail below, the combination of trace elements of the current claims have unique trace element combinations and unique doses of active ingredients of zinc, copper, manganese, and selenium per 1 mL of the formulation and low or no impurities of chromium and aluminum. These unique combinations and doses of trace elements are new[1] and are designed to provide safe and effective trace element supplementation from a single all-in-one injectable product for a majority of patients, which reduces labor time and medication errors compared with using multiple separate single-entity trace element formulation products. These unique combinations and doses of trace elements of the current claims were selected out of hundreds of different combinations of trace elements and doses that are not disclosed in the art and are not made obvious by it. This includes those that the Office cites-- Multitrace® 5 references and Burjonrappa. (See Declaration of Dr. Joseph I. Boullata at Paragraphs 9-45.)

These hundreds of different combinations of trace elements and different doses in the art cover a very large number of distinct compositions having varied combinations and dosages of trace elements, and Applicant had to select from this very large number of dosages and combinations of trace elements, and even if one selects these combinations of trace elements and doses from this very large number of choices, one still does not obtain the current claims. The Office should consider the seminal case of *Genetics Institute LLC v. Novartis Vaccines and Diagnostics Inc.*, 655 F.3d 1291 (Fed. Cir. 2011), where the CAFC ruled if the disclosed range is so broad as to encompass a very large number of possibly distinct compositions, the invention is not routine optimization. See *Genetics Institute LLC v. Novartis Vaccines and Diagnostics Inc.*, 655 F.3d 1291 (Fed. Cir. 2011).

[1] In the Office Action, the Examiner also concedes that they are new compositions. (Office Action at Page 7).

Further, these unique combinations and doses of trace elements of the current claims satisfied a long felt, but unmet, need for safe and effective trace element supplementation that persisted for years in the art, achieved wide spread use and commercial success that was not the result of routine optimization. They were also the first FDA approved combination trace element products. (See Declaration of Dr. Joseph I. Boullata at Paragraphs 20, 23, and 43-45 and Declaration of Ms. Joann Gioia at Paragraphs 7, 8 and 10.)

For some background information for the Examiner, combination trace element products are referred to in the art as "bundled packages" or "cocktails"[2]. They allow the combination of trace elements to be injected via a single injection. When a health care provider (e.g., one of ordinary skill in the art) decides to treat a patient with a combination trace element product, the health care provider is looking to supplement multiple trace elements and not just one. Thus, if a patient required a different dose of one (or more) trace elements found in the bundled package or cocktail, one of ordinary skill in the art would instead use one (or more) single trace element formulation products for this patient. The tradeoff would be that with single trace element formulation products, there would be multiple injections into the parenteral nutrition (PN) and possibly more risk of potential medication errors and bacterial contamination from the multiple injections into the PN port; however, the individual supplementation needs of that particular patient would be better met. Therefore, "bundle packages" of combination trace element products are completely different from single trace element formulations for a person of ordinary skill in the art. See Declaration of Dr. Joseph I. Boullata at Paragraphs 18, 23-25 and 26.

In the Office Action, the Office asserts that "one of ordinary skill in the art would be equally motivated to formulate a composition comprising the instantly claimed elements in the instantly claimed amounts not by diluting Multitrace® 5 [but] looking to Multitrace® 5 as a **'blueprint to form a new composition'** and [adjusting] it for the nutritional needs of the patient to be treated. That is if one of ordinary skill in the art has a patient needing nutritional supplementation of zinc, copper, selenium, and manganese but no chromium, **aluminum**, iron, and/or vitamins, one of ordinary skill in the art would be able to make such a composition" (Office Action at Page 7 and emphasis added).

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[2] See Burjonrappa Abstract and Declaration of Dr. Joseph I. Boullata at Paragraph 18.

The Office appears on one hand to be asserting that Multitrace® 5 can be used as a "blue print", but that the individual trace elements in Multitrace® 5 can be adjusted based on a patient's need as if Multitrace® 5 was not a bundled package of trace elements but a single trace element product.

Applicant respectfully submits that this is an incorrect interpretation of the Multitrace® 5 references and a person of ordinary skill in the art would not interpret the older Multitrace® 5 references in this way for at least five reasons. See Declaration of Dr. Joseph I. Boullata at Paragraphs 18, 23, 24, 25 and 26.

First, regarding supplementing aluminum based on nutritional needs of a patient as asserted by the Office, one of ordinary skill in the art would never intentionally consider supplementing aluminum to a patient. Aluminum is a toxicant of serious concern to be avoided as much as practical. See Declaration of Dr. Joseph I. Boullata at Paragraph 17.

Second, the Multitrace® 5 and Multitrace® 5 Concentrate products mentioned in the Office Action are not FDA approved products so in designing the Tralement® combination trace element product (e.g., in claim 1) and Multrys® combination trace element product (e.g., claim 81), why would a person of ordinary skill in the art start with them as a blueprint? See Declaration of Dr. Joseph I. Boullata at Paragraphs 18, and 24-26.

Third, the currently claimed doses of the active ingredients zinc, copper, manganese, chromium and selenium per 1 mL of the formulation cannot have a single trace element dose reduced or increased without similar increases or decreases in the other trace elements in the bundle package. One cannot dilute or remove just one trace element without diluting or removing the other trace elements that is the point of using a bundle package of trace elements versus using a single trace element so it is not just a matter of dilution or removal but the fact that if the decision is made to use a bundle package of trace elements one skilled in the art, typically is not considering using one individual trace element by itself without increasing or decreasing the other trace elements in that bundle package as well. See Declaration of Dr. Joseph I. Boullata at Paragraph 16.

If a person of ordinary skill in the art wanted to increase or decrease one of the doses of the individual trace elements in the bundle package based on the nutritional needs of the patient, one typically would not use a bundle package of trace elements in the first place that included that

particular trace element that needed adjustment but instead use one (or more) single trace element formulation products for that patient, which would defeat the purpose of using a bundled package of trace elements in the first place. See Declaration of Dr. Joseph I. Boullata at Paragraph 23.

Fourth, it is not a question of whether one skilled in the art would be able to make such a composition as asserted by the Office on Page 7 of the Office Action, but rather there must be some disclosure in the cited references to do so. Here there is no disclosure, teaching or suggestion to reduce or increase the Multitrace® 5 references to obtain the combination of trace elements and doses per 1 mL of the current claims. Again, if one wanted to increase, remove or decrease a trace element from a bundle package, one would not be inclined to use it in the first place.

More particularly, the difference between the unapproved products Multitrace® 5, Multitrace Concentrate and the now FDA approved formulations (Tralement® and Multrys®) claimed in the patent application are compared below in Tables A and B.

Table A

Multitrace® 5 Active Ingredient (Per 1 mL) Not FDA Approved	**(17/365,695) Claim 1 Active Ingredient (Per 1 mL) Tralement® FDA Approved**	**Multitrace® 5 Concentrate Active Ingredient (Per 1 mL) Not FDA Approved**
Zinc 1000 mcg	Zinc about **3000 mcg**	Zinc 5000 mcg
Copper 400 mcg	Copper about **300 mcg**	Copper 1000 mcg
Manganese 100 mcg	Manganese about **55 mcg**	Manganese 500 mcg
Chromium 4 mcg	**No added Chromium**	Chromium 10 mcg
Selenium 20 mcg	Selenium about **60 mcg**	Selenium 60 mcg

Table A shows that, in contrast to Multitrace® 5, the formulation of, for example, claim 1 has no added chromium to it. In addition to no added chromium, the amount of elemental zinc and selenium are 3 times more than that of Multitrace® 5, while the copper is less and the manganese is almost half as much as that of Multitrace® 5 per 1 mL. See Declaration of Dr. Roshan James at Paragraph 9.

The Multitrace® 5 Concentrate formulation has added chromium, over 1.6 times more elemental zinc, over 3 times more elemental copper, over 9 times more elemental manganese per 1 mL compared to the unique formulation of, for example, claim 1. The amount of selenium (60 mcg) in Multitrace® 5 Concentrate is the same concentrated amount of 60 mcg as that of the unique formulation of, for example, claim 1. In claim 96 of the current application, the ratio of elemental copper to elemental zinc here is 1:10 (e.g., claim 96). This ratio is also not found in the cited references. See Declaration of Dr. Roshan James at Paragraph 10.

On review of these differences, the formulation of, for example, claim 1 is far from what would be considered routine optimization and would not be obvious. Moreover, the older Multitrace® 5 and Multitrace® 5 Concentrate would not be used as a "blueprint" to design the trace elements formulation of, for example, claim 1. See Declaration of Dr. Roshan James at Paragraph 11.

For neonatal patients, the combination of trace elements of the current claims, now in, for example, claim 81, would also not be obvious. The difference between Multitrace® 4 Pediatric, and Multitrace® Neonatal, which were also not FDA approved, and the neonatal formulation of, for example, claim 81, Multrys® which is now FDA approved, are compared below in Table B.

Table B

Multitrace® 4 Pediatric Active Ingredient (Per 1 mL) Not FDA Approved	**(17/365,695) Claim 81 Active Ingredient (Per 1 mL) Multrys® Neonatal FDA Approved**	**Multitrace® 4 Neonatal Active Ingredient (Per 1 mL) Not FDA Approved**
Zinc 1000 mcg	Zinc about **1000 mcg**	Zinc 1500 mcg
Copper 100 mcg	Copper about **60 mcg**	Copper 100 mcg
Manganese 25 mcg	Manganese about **3 mcg**	Manganese 25 mcg
Chromium 1 mcg	**No added Chromium**	Chromium 0.85 mcg
No added Selenium	Selenium about **6 mcg**	No added Selenium

In contrast to Multitrace® 4 Pediatric, the neonatal formulation of, for example, claim 81

per 1 mL has no added chromium to it as shown in Table B above. In addition to no added chromium, the amount of elemental zinc is the same in both formulations. Multitrace® 4 Pediatric has 1.6 times more copper and over 8 times more manganese as compared to the neonatal formulation of, for example, claim 81. Multitrace® 4 Pediatric has no added selenium to it, however, the neonatal formulation of, for example, claim 81 has 6 mcg of selenium per 1 mL.

The Multitrace® 4 Neonatal formulation per 1 mL has added chromium, 1.5 more elemental zinc, 1.6 times more copper and over 8 times more manganese as compared to the neonatal formulation of, for example, claim 81. Multitrace® 4 Neonatal has no added selenium to it, however, the neonatal formulation of, for example, claim 81 has 6 mcg of selenium per 1 mL.

Again, it is not simply a matter of removing chromium from Multitrace® 4 Pediatric and Multitrace® 4 Neonatal formulations and lowering the amounts of other trace elements in the new formulation. There were changes made to the copper, manganese and selenium, which was also incorporated into the neonatal formulation of, for example, claim 81. Also, the ratio of elemental selenium to elemental copper is 1:10 (e.g., claim 98), which is not found in the cited references.

The unique combination trace elements (as recited in, for example, claims 1 and 81) for use in adults, pediatric and/or neonatal patients, better meet the needs of a majority of patients (see American Regent FDA announcement September 30, 2020, Exhibit G). In essence, new unique combination trace elements have been made that meet a majority of individuals' trace elements needs in 1 mL that would, in the past, require multiple injections of separate single-entity trace element formulation products to meet these needs in the PN. These new unique combination of trace elements and doses of, for example, claims 1 and 81 are far from routine optimization. Again, they provide the safe and effective trace element supplementation from a single all-in-one injectable product, which reduces labor time and medication errors compared with using multiple separate single-entity trace element formulation products. It also reduces the number of injections into the PN container and provides a reduced chance of bacterial contamination and particulate formation in the PN because there are now a reduced number of entries into the PN injection port. See Declaration of Dr. Joseph I. Boullata at Paragraphs 18, 23-25 and 26.

Fifth, if the Office is asserting that the combination of trace elements and doses per 1 mL can be made from scratch, then there has to be some disclosure, teaching or suggestion to do so in the Multitrace® 5 references at the concentration and doses claimed per 1 mL, which there is clearly not.

Applicant submits that the product information labeling of Multitrace® 5 and Multitrace® 5 Concentrate does indeed disclose periodic monitoring of plasma levels of chromium. However, these product information labels do not disclose removing chromium from the Multitrace® 5 and Multitrace® 5 Concentrate formulations as that of the formulation of, for example, claims 1 and 81. See Declaration of Dr. Joseph I. Boullata at Paragraphs 14-17 and Declaration of Dr. Roshan James at Paragraphs 8-15.

Further, the product information labeling of Multitrace® 5 and Multitrace® 5 Concentrate also indeed disclose periodic monitoring of plasma levels of zinc, copper, manganese, and selenium in addition to chromium. However, the product information labeling of Multitrace® 5 does not disclose making the amount of elemental zinc and selenium 3 times more than that of Multitrace® 5, and making the elemental copper less and elemental manganese almost half as much as that of Multitrace 5 per 1 mL.

Regarding the Multitrace® 5 Concentrate formulation, the product information labeling also does not disclose making elemental zinc over 1.6 times less, elemental copper over 3 times less and elemental manganese over 9 times less per 1 mL as in the formulation of, for example, claim 1. Additionally, the amount of selenium (60 mcg) in Multitrace® 5 Concentrate is the same concentrated amount of 60 mcg as that of the formulation of claim 1. See Declaration of Dr. Joseph I. Boullata at Paragraphs 14-17.

Applicant's compositions with the unique combination of trace elements at the specific doses are new compositions not known in the cited art and are therefore not the result of routine optimization and would not have been obvious to a person of ordinary skill in the art. Therefore, withdrawal and reconsideration of the rejections of claims 1-18, 65-71, and 74-77 under 35 U.S.C. § 103(a) is respectfully requested.

B. Burjonrappa in Combination With Multitrace® 5 and Multitrace® 5 Concentrate Do Not Make the Current Claims Obvious

The Office uses Burjonrappa for teaching reducing chromium supplementation (at page 767) and combines this reference with the Multitrace® 5 references to conclude that claims 1-18, 65-71, and 74-77 are allegedly obvious and are the result of routine optimization. Applicant respectfully disagrees with the Office.

As an initial matter, the Office concedes that the current claims include combinations and doses of trace elements that are new. However, in the Office Action at Page 9, the Office cites "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Applicant respectfully disagrees with the Office and submits that the general conditions mentioned in *In re Aller* are not met here.

For example, as discussed above, the Multitrace® 5 references do not disclose, teach or suggest removing chromium from the bundled package of trace elements, only to monitor it along with the other trace elements. Further, the Multitrace® 5 references do not disclose, teach or suggest the combination of active trace elements and their doses as currently claimed. Burjonrappa does not remedy this defect.

Burjonrappa is a general review on physiology and requirements of individual trace elements in neonates. Burjonrappa does not disclose or teach that selenium is missing from the available neonatal products of that time. See Declaration of Dr. Joseph I. Boullata at Paragraph 25. This is in contrast to the currently claimed combination trace element products that all have selenium in them. Therefore, this is at least one general condition from *In re Aller* that is not met.

Regarding chromium, and as the Office notes, Burjonrappa discloses that some experts question the actual need for chromium supplementation in neonates. See Office Action at Page 9. However, Burjonrappa clearly states:

> The current consensus remains that Cr supplementation is **important** in individuals needing PN.

(See Burjonrappa at Page 767 Left Column, and emphasis added.) Thus, there is no disclosure to completely remove chromium from the "bundled package" of trace elements that Burjonrappa refers to. This is a second general condition from *In re Aller* that is not met.

Moreover, Burjonrappa also discloses certain schedules for starting various trace

elements. For example, according to Burjonrappa, zinc supplementation is started at the initiation of PN. Other trace elements can be added to the PN in 2-4 weeks after initiation. According to Burjonrappa, copper and manganese need to be withheld if the neonate develops PN-associated liver disease (see Burjonrappa's Results in the Abstract).

Because various trace elements are administered at different time frames, Burjonrappa is teaching adding individual trace elements separately at certain days of the PN administration and not using bundled packages of trace elements. This is particularly so as Burjonrappa discusses in his conclusion that in certain settings it may be more appropriate to individualize trace element supplementation based on the predetermined physiologic needs of the patient rather than using "bundled packages of trace elements as is the current norm" (see Burjonrappa's Conclusion in the Abstract). The take away from Burjonrappa is that bundled packages of trace elements are not good for customization of an individual trace element based on a patient's individual supplementation needs.

Because the Multitrace® 5 references are bundled packages of trace elements and Burjonrappa is directed to single trace element products, these references are incompatible with each other and a person of ordinary skill in the art would not combine these references together the way the Office does. Moreover, Burjonrappa teaches that the consensus remains that chromium supplementation is **important** in individuals needing PN. However, the current claims do not have chromium as an active ingredient, but instead have no chromium or chromium as a contaminant. See Declaration of Dr. Joseph I. Boullata at Paragraphs 19 and 24-26.

Furthermore, based on the references cited by the Office, it appears that the Office is using improper hindsight reconstruction in the rejections. To that end, Applicant cautions the Office against the use of hindsight reconstruction. In the CAFC case of *Mintz v. Dietz & Watson, Inc.,* 679 F.3d 1372 (Fed. Cir. 2012) "hindsight" is mentioned repeatedly in the case, and the court warned against "the forbidden use of hindsight" and the "prohibited reliance on hindsight," as well as the need for "a court to walk a tightrope blindfolded (to avoid hindsight)." Additionally, MPEP 2142, states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." As such, given that there is nothing in the art that would motivate one of ordinary skill in the art to combine

those references in the manner suggested by the Office, it is apparent that the rejection is based on improper hindsight recreation of the claims using the teachings of the present application as a road map.

In summary, Applicant's compositions with the unique combination of trace elements at the specific doses are new compositions not known in the cited art and are therefore not the result of routine optimization and would not have been obvious to a person of ordinary skill in the art. Therefore, withdrawal and reconsideration of the rejections of claims 1-18, 65-71, and 74-77 under 35 U.S.C. § 103(a) is respectfully requested.

C. Comparative Data Showing Unexpected Reduced Elemental Impurities and Improved Lower Bacterial Endotoxin Limits

Head to head comparative tests to determine levels of elemental impurities of the Tralement® formulation of, for example, claim 1 were compared to the Multitrace® 5 Concentrate formulation (cited by the Examiner and which contains, among other things, 10 mcg/mL of elemental chromium as an active ingredient). The results of these tests are summarized in Table E below and discussed in the Declaration of Dr. Roshan James at Paragraphs 16-21.

Table E

Description	Trace Element Injection-5 1 mL SDV (with chromium) (Multitrace® 5 Concentrate)- commercial lot	Trace Element Injection-4 1 mL SDV (Tralement®) No Added Chromium- commercial lot	Trace Element Injection-5 1 mL SDV (Multitrace® 5 Concentrate)- laboratory batch	Trace Element Injection-4 1 mL SDV (Tralement®)- No added Chromium - laboratory batch.
Vial	2 mL Flint Type I USP Tubular Vial 13 mm Finish Sulfur Treated (Gerresheimer)			
Stopper	13 mm, 4588/40 Gray, Silicone Level 3 Coating (West Pharma)	13 mm, 4432/50 Gray, WPS-S2-F451, B2-40 Coating (West Pharma)	13 mm, 4432/50 Gray, WPS-S2-F451, B2-40 Coating (West Pharma)	13 mm, 4432/50 Gray, WPS-S2-F451, B2-40 Coating (West Pharma)
Lot #	0080	0329	14RDL230330-3	14RDL230330-2
Mfg. Date	04/20/2020	10/14/2020	03/30/2023	03/30/2023
Storage Condition	Controlled Room Temperature	Controlled Room Temperature	N/A	N/A

Timepoint of Testing	2 Years 11 Months from manufacture (03/31/2023)	2 Years 5 Months from manufacture (03/31/2023)	04/18/2023	04/18/2023
Elemental Impurity				
B[1] NMT 50 ppm	1.2	1.8	<1.0	< 1.0
Na NMT 24,000 ppm	1.5	1.9	2.2	1.9
Mg NMT 50 ppm	0.4	< 0.1	0.1	< 0.1
Al NMT 6.0 ppm	**0.3**	**0.2**	0.1	0.1
Si NMT 100 ppm	**18.0**	**3.1**	**1.9**	**< 1.0**
K NMT 94,000 ppm	0.1	< 0.1	0.1	0.9
Ca NMT 50 ppm	3.6	< 0.1	0.1	0.1

N/A = Not Applicable NMT = Not More Than ppm = parts per million
[1]Elements Analyzed: B = Boron Na = Sodium Mg = Magnesium Al = Aluminum Si = Silicon K = Potassium Ca = Calcium

In Table E, the commercial lots of Multitrace® 5 Concentrate unexpectedly had almost six times more silicon in it compared to the Tralement® formulation of, for example, claim 1. Also, in the commercial lots, there was 1.5 times more aluminum in Multitrace® 5 Concentrate compared to the Tralement® formulation of, for example, claim 1. To confirm this result, Multitrace® 5 Concentrate and Tralement® laboratory batches were tested and the trend for the higher silicon impurity also continued where Multitrace® 5 Concentrate unexpectedly had more than double the amount of silicon in it in just over two weeks compared to the Tralement® formulation of, for example, claim 1. Therefore, Multitrace® 5 Concentrate, among other things, has higher amounts of elemental impurities such as silicon and aluminum, is of poorer quality, and is less stable when compared to the Tralement® finished drug product. See Declaration of Dr. Roshan James at Paragraphs 18-21.

Of note, new claims 99 and 100 have been added to specifically recite that the impurity is silicon.

Injectable pharmaceutical products are tested for the presence of endotoxins in what is called a Bacterial Endotoxins Test (BET). The BET is an *in vitro* assay for detection and quantitation of bacterial endotoxins that can be a component of the cell wall of gram-negative bacteria. If endotoxins are present in the injectable formulation, they can lead to a pyrogenic response (e.g., contaminants that can cause a fever) or sepsis in a patient. Typically, endotoxins are measured in Endotoxin Units per milliliter (EU/mL). See Declaration of Dr. Roshan James at Paragraph 22. Table F below compares the BET of the older Multitrace® 5 Concentrate formulation to the new Tralement® and Multrys® formulations.

Table F

Formulation	**Bacterial Endotoxins Test (BET)**
Tralement® (e.g., claim 1)	Not more than 50 EU/mL
Multrys® (e.g., claim 81)	Not more than 16.67 EU/mL
Multitrace® 5 Concentrate	Not more than 125 EU/mL

The BET limit for Multitrace® 5 Concentrate was at a range of not more than (NMT) 125 EU/mL. However, if the Tralement® formulation (e.g., claim 1) and the Multrys® (e.g., claim 81) were at this BET range, they would not be approved by the FDA. The Tralement® formulation has a more stringent limit of NMT 50 EU/mL, which is 2.5 times less than Multitrace® 5 Concentrate. The Multrys® formulation has an even more stringent limit of NMT 16.67 EU/mL, which is over 7 times less than Multitrace® 5 Concentrate. See Declaration of Dr. Roshan James at Paragraph 23.

Of note, new claims 103 and 104 have been added to specifically recite that the injectable composition has an EU/mL limit of not more than 50 EU/mL or a bacterial endotoxin limit of less than 17.50 EU/mL, respectively.

Accordingly, Applicant's compositions with the unique combination of trace elements at the specific doses are new compositions, that have unique stability and purity profiles, and also have significantly improved properties such as lower EU/mL, which are not the result of routine optimization and would not have been obvious to a person of ordinary skill in the art. See the Declaration of Dr. Roshan James at Paragraphs 16-23.

D. The New Trace Elements Formulations Meet a Long Felt and Persistent Need

Applicant also submits that the unique combinations and specific dosages of trace elements of the current claims (e.g., claims 1 and 81) satisfied a long felt, but unmet, need in the art for safe and effective trace element supplementation that persisted for over 8 years without solution until the filing of the current application and are therefore not the result of routine optimization and would not have been obvious to a person of ordinary skill in the art.

To establish long felt need, Applicant must establish that (1) an art recognized need existed for a long period of time without solution; (2) the long felt need was not satisfied by another before the invention by the inventor; and (3) the invention satisfies that long-felt need. *Leo Pharmaceutical Products, Ltd. v. Rea,* 726 F. 3d 1346 (Fed. Cir. 2013) and MPEP 716.04.

Regarding the long felt need, items (1), (2) and (3) above, even Burjonrappa, which the Office cites to in the rejection, recognized the need back in April of 2012 for an "ideal mix" of different trace elements that would not provide excessive amounts of other trace elements:

> Of note, **no trace element package currently available in North America** provides the **'ideal mix'** of the different trace metals, necessitating the addition of individual intravenous trace element solutions to the TPN solution to meet the increased needs of 1 trace mineral **while not providing excessive amounts of another**.

See Burjonrappa's conclusion at Page 769. Burjonrappa was not the only one to identify the long felt need that the available combination trace element products at that time including the Multitrace® 5 references cited by the Office provided excessive amounts of some trace elements, the American Society for Parenteral and Enteral Nutrition (ASPEN) also identified this problem.

ASPEN is a society of dietitians, nurses, pharmacists, physicians and scientists involved in providing clinical nutrition to patients. In 2009, 2011, 2012, 2014 and 2015, ASPEN gave honors and awards to Dr. Joseph I. Boullata, a person of ordinary skill in the art. With this response to the Office Action, Dr. Boullata provides the reasons that the claims are not obvious in his declaration as discussed herein. See Declaration of Dr. Joseph I. Boullata at Paragraphs 3-45.

In 2012, ASPEN published a position paper on recommended changes that needed to be made to available combination trace element products. See "A.S.P.E.N. position paper:

Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products," Nutrition in Clinical Practice, Vol. 27, No. 4 (August 2012), pp. 440-491 (ASPEN 2012), which is already of record and attached as Exhibit B.

ASPEN 2012 provides adult, pediatric and neonatal parenteral daily recommendations for trace elements in Tables 4, 6, and 7. Also, Table 10 shown below lists available parenteral combination trace element products at that time in North America including, among others, Multitrace® 5 and Multitrace® 5 Concentrate for adults that the Office refers to in the Office Action, and other formulations for pediatric and neonatal patients. Table 13 also shown below lists those combination trace element products available in Europe.

Table 10. Parenteral Multi–Trace Element Products Available in North America

Product (Distributor)	Content per mL	Zinc, mg (μmol)	Copper, mg (μmol)	Chromium, mcg (μmol)	Manganese, mg (μmol)	Selenium,[a] mcg (μmol)	How Supplied
Adults							
Multitrace-4 (American Regent)	1 mL	1 (15.3)	0.4 (6.29)	4 (0.08)	0.1 (0.0018)	0 (0)	10-mL MDV
Multitrace-4 Concentrate (American Regent)	1 mL	5 (76.48)	1 (15.73)	10 (0.2)	0.5 (0.0091)	0 (0)	1-mL SDV and 10-mL MDV
4-Trace Elements (Hospira)	5 mL	4 (61.18)	1 (15.73)	10 (0.2)	0.8 (0.0146)	0 (0)	5-mL SDV and 50-mL MDV
Multitrace-5 (American Regent)	1 mL	1 (15.3)	0.4 (6.29)	4 (0.08)	0.1 (0.0018)	20 (0.25)	10-mL MDV
Multitrace-5 Concentrate (American Regent)	1 mL	5 (76.48)	1 (15.73)	10 (0.2)	0.5 (0.0091)	60 (0.76)	1-mL SDV and 10-mL MDV
Neonatal and Pediatrics							
Multitrace-4 Neonatal (American Regent)	1 mL	1.5 (22.94)	0.1 (1.57)	0.85 (0.02)	0.025 (0.0005)	0 (0)	2-mL SDV
Multitrace-4 Pediatric (American Regent)	1 mL	1 (15.3)	0.1 (1.57)	1 (0.02)	0.025 (0.0005)	0 (0)	3-mL SDV
Trace Elements Injection 4, USP—Pediatric (American Regent)	1 mL	0.5 (7.65)	0.1 (1.57)	1 (0.02)	0.03 (0.0006)	0 (0)	10-mL MDV

MDV, multiple-dose vial; SDV, single-dose vial; USP, United States Pharmacopeia. Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently.

Table 13. Parenteral Multi-Trace Element Products Available in Europe

Product (Distributor)	Content per mL	Zinc, mg (µmol)	Copper, mg (µmol)	Chromium, mcg (µmol)	Manganese, mg (µmol)	Selenium, mcg (µmol)	Molybdenum, mcg (µmol)	Iron, mg (µmol)	Iodide, mg (µmol)	Fluoride, mg (µmol)	Cobalt, mcg (µmol)	How Supplied
Adults												
Addaven (Fresenius Kabi)	10 mL	6.5 (99.4)	1.24 (19.5)	10 (0.2)	0.275 (5.0)	32 (0.41)	19 (0.2)	1.1 (19.7)	0.13 (1)	0.95 (50)	0 (0)	10-mL ampule
Decan (Baxter & Laboratoires Aguettant)	40 mL	10 (153)	0.48 (7.5)	15 (0.3)	0.200 (3.6)	70 (0.89)	25 (0.26)	1 (17.9)	0.0015 (0.012)	1.45 (76.3)	1.47 (0.025)	40-mL ampule
Tracutil (B.Braun)	10 mL	3.3 (50)	0.76 (12)	10 (0.2)	0.55 (10)	24 (0.3)	10 (0.1)	2.0 (35)	0.127 (1)	0.57 (30)	0 (0)	10-mL ampule
Pediatrics and Neonates												
Peditrace (Fresenius Kabi)	1 mL	0.25 (3.82)	0.02 (0.32)	0 (0)	0.001 (0.02)	2 (0.03)	0 (0)	0 (0)	0.001 (0.008)	0.06 (3)	0 (0)	10-mL ampule
Inzolen-Infantibus sine NaK (Kohlpharma)	1 mL	0.097 (1.48)	0.032 (0.5)	8 (0.15)	0.027 (0.5)	0 (0)	0 (0)	0.091 (1.63)	0 (0)	0 (0)	14 (0.24)	10-mL ampule
Oligo-elementi Aguettant Pediatrique (Aguettant)	1 mL	0.1 (1.53)	0.03 (0.47)	2 (0.04)	0.01 (0.2)	5 (0.06)	5 (0.05)	0.05 (0.9)	0.005 (0.04)	0.05 (2.63)	1.5 (0.03)	10-mL ampule

Information based on manufacturer's labeling information as of February 1, 2010. Manufacturers, products, and product information can change frequently.

Using ASPEN 2012 (e.g., Tables 10 and 13) as a guide, there are potentially **more than six hundred different formulations** that can be made with different combinations of trace elements and different doses per 1 mL. Notwithstanding ASPEN 2012, there are no adult formulations that disclose as active ingredients about 3,000 µg of zinc, about 300 µg of copper, about 60 µg of selenium, and about 55 µg of manganese without added chromium per 1 mL in an all-in-one trace element combination product as in, for example, claim 1. Also, ASPEN 2012 does not disclose pediatric or neonatal formulations with the active ingredients of about 1000 µg of zinc, 60 µg of copper, 6 µg of selenium and 3 µg of manganese and no added chromium per 1 mL in an all-in-one trace element combination product as in, for example, claim 81. The unique combination and doses of trace elements of the current claims were selected out of hundreds of different combinations of trace elements and doses that are not disclosed in the art and are not made obvious by it. See Declaration of Dr. Joseph I. Boullata at Paragraphs 27-32.

Notwithstanding the more than six hundred different formulations, ASPEN 2012 also identifies a need that the parenteral combination trace element products commercially available in the U.S. as of 2012 require "**significant modifications**" (see ASPEN 2012 Abstract) and that **"safer and more effective"** vitamin and trace element products are needed (see ASPEN 2012 at Page 455). Therefore, like Burjonrappa, ASPEN 2012 identifies a long felt need for new

combination trace element products and that those currently on the market in 2012 required "significant modifications."

This long felt need persisted in 2015 with still no solution and, as a result, ASPEN published a Special Report entitled "A Call to Action to Bring Safer Parenteral Micronutrient Products to the U.S. Market" (August 2015), pp. 559-569 (ASPEN 2015), attached as Exhibit C.

ASPEN 2015 also discloses the potential toxicities of the then available parenteral combination trace element products in North America. In Table 4 of ASPEN 2015 shown below, there are listed six available parenteral combination trace element products as of 2015 in North America for adults including Multitrace® 4/5 (3 mL daily dose), Multitrace® 4/5 Concentrate (1 mL daily dose), 4-Trace Elements® (5 mL daily dose), Addamel N® and the ASPEN recommendations. Table 4 is reproduced below.

Table 4. Comparison of Adult Multi-Trace Element Products Available in the U.S. and A.S.P.E.N.-Recommended Changes [97]

	MULTI-TE PRODUCTS AVAILABLE IN U.S.				TEMPORARY U.S. IMPORTATION[98]
Trace Elements	Multitrace-4/-5® (MTE4/5) (3 mL daily dose)	Multitrace-4/-5 (MTE4/5) Concentrate® (1 mL daily dose)	4-Trace Elements® (5 mL daily dose)	A.S.P.E.N. Recommendations	Addamel N® (10 mL daily dose)
Zinc (Zn)	3 mg	5 mg	4 mg	No changes (3–5 mg)[99]	6.5 mg
Copper (Cu)	1.2 mg	1 mg	1 mg	Decrease to 0.3–0.5 mg	1.3 mg
Manganese (Mn)	0.3 mg	0.5 mg	0.8 mg	Decrease to maximum of 0.055 mg	0.27 mg
Chromium (Cr)	32 mcg	10 mcg	10 mcg	10 mcg sufficient for most patients but need product without Cr for patients prone to Cr toxicity	16 mcg
Selenium (Se)	9 mcg (MTE4) 60 mcg (MTE5)	9 mcg (MTE4) 60 mcg (MTE5)	0 mcg	60–100 mcg (dose higher than 60 mcg preferred)	32 mcg
Iron (Fe)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid containing PN	1.1 mg
Molybdenum (Mo)	—	—	—	Insufficient data to recommend routine administration	19 mcg
Iodide (I)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed	130 mcg
Fluoride (F)	—	—	—	Routine supplementation of PN could be beneficial, but more research is needed	950 mcg
Vial size	10-mL multi-dose vials	1-mL single and 10-mL multi-dose vials	5-mL single and 50-mL multi-dose vials	—	10-mL single dose
Manufacturer	American Regent (Shirley, NY)	American Regent (Shirley, NY)	Hospira (Lake Forest, IL)	—	Fresenius Kabi(Lake Zurich, IL)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; FDA, U.S. Food and Drug Administration; PN, parenteral nutrition; TE, trace elements; U.S., United States.
[98] 5/29/2013 FDA granted temporary importation due to a shortage of multi-TE products.
[99] A.S.P.E.N. recommendations in the original position paper were for no changes in the standard products available in the U.S., which as shown in this table was 3–5 mg/day.

From Table 4, ASPEN 2015 recommends that routine supplementation with iron, iodide, and fluoride could be beneficial, yet Applicant here did not add as active ingredients iron, iodide, and/or fluoride to their unique formulations in, for example, claims 1 and 81 even though

the ASPEN 2015 guidelines recommend that those trace elements may be beneficial.

Regarding chromium and selenium for adults and some pediatric patients, the ASPEN 2015 guidelines, also **recommends that chromium 10 mcg is sufficient for most patients and selenium doses higher than 60 mcg are preferred** (see the bolded arrows in Table 4 above). However, Applicant again did more than just merely follow the guidelines and decided not to add chromium, and kept the selenium at the less preferred 60 mcg dose (see, for example, claim 1). Therefore, what Applicant did was more than routine optimization of a formulation. See Declaration of Dr. Joseph I. Boullata at Paragraphs 34-36.

Regarding, pediatric and neonatal patients, in Table 5 of ASPEN 2015, there are also listed, as of that time, currently available parenteral multitrace element products in the North America for pediatric and neonatal patients dosed by weight and age including, among others, Multitrace® 4 Neonatal (1 mL daily dose), Multitrace® 4 Pediatric (1 mL daily dose), Trace Elements 4 injection Pediatric (1 mL daily dose), Peditrace® (per 1 mL) and the ASPEN recommendations. Table 5 is reproduced below.

Table 5. Comparison of Pediatric/Neonatal Multi-Trace Element Products Available in the U.S. and the A.S.P.E.N.-Recommended Changes.[^]

	MULTI-TE PRODUCTS AVAILABLE IN U.S. (Manufacturer Dosing Recommendations)				TEMPORARY U.S. IMPORTATIONS[#]
Trace Elements	Multitrace-4 Neonatal® (per 1 mL)	Multitrace-4 Pediatric® (per 1 mL)	Trace Elements Injection 4 USP-Pediatric® (per 1 mL)	A.S.P.E.N. Recommendations	Peditrace® (per 1 mL)
Zinc (Zn)	1.5 mg (0.1 mg/kg/d, 0.3 mg/kg/d premature infants <3 kg)	1 mg (0.1 mg/kg/d)	0.5 mg (0.1 mg/kg/d)	No change (0.3 mg/kg/d premature infants <3 kg and 0.1 mg/kg/d for infants/children >3 kg)[^^]	0.25 mg (0.25 mg/kg/d ≤15 kg, 2.75 mg/d >15 kg)[^^^]
Copper (Cu)	0.1 mg (0.02 mg/kg/d)	0.1 mg (0.02 mg/kg/d)	0.1 mg (0.02 mg/kg/d)	0.02 mg/kg/d	0.02 mg (0.02 mg/kg/d ≤15 kg, 0.3 mg/d >15 kg)[^^^]
Manganese (Mn)	25 mcg (2–10 mcg/kg/d)	25 mcg (2–10 mcg/kg/d)	50 mcg (2–10 mcg/kg/d)	Decrease to 1 mcg/kg/d in neonates with maximal daily dose in pediatrics to 55 mcg/day	1 mcg (1 mcg/kg/d ≤15 kg, 15 mcg/d >15 kg)[^^^]
Chromium (Cr)	0.85 mcg (0.14–0.20 mcg/kg/d)	1 mcg (0.14–0.20 mcg/kg/d)	1 mcg (0.14–0.20 mcg/kg/d)	➡ Reduce dose to values shown in Table 6 and have product available without Cr for patients at increased risk of toxicity	0 mcg
Selenium (Se)	6 mcg	6 mcg	6 mcg	➡ Add with dose of 2 mcg/kg/d	2 mcg (2 mcg/kg/d ≤15 kg, 20 mcg/d >15 kg)[^^^]
Iron (Fe)	----	----	----	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid-containing PN	----
Molybdenum (Mo)	----	----	----	Insufficient data to recommend routine administration	----
Iodide (I)	----	----	----	➡ Routine supplementation of PN could be beneficial, but more research is needed	1 mcg (1 mcg/kg/d ≤15 kg, 10 mcg/d >15 kg)[^^^]
Fluoride (F)	----	----	----	Routine supplementation of PN could be beneficial, but more research is needed	27 mcg (27 mcg/kg/d ≤15 kg, 55 mcg/d >15 kg)[^^^]
Vial size	2-mL vials	5-mL vials	10-mL amber glass vials	----	10-mL vials
Manufacturer	American Regent (Shirley, NY)	American Regent (Shirley, NY)	American Regent (Shirley, NY)	----	Fresenius Kabi (Lake Zurich, IL)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; FDA, U.S. Food and Drug Administration; PN, parenteral nutrition; TE, trace element; U.S., United States.
[#]As of 2/2/2021 FDA granted temporary importation due to a shortage of multi-TE products.
[^]A.S.P.E.N. did not recommend any changes to the multi-TE products available in the U.S., and as shown in this table, the available products recommend 0.3 mg/kg/d for premature infants <3 kg and 0.1 mg/kg/d for infants and children ≥3 kg.
[^^]Manufacturer dosing recommendations are 1 mL Peditrace/kg/d for infants and children with weight up to 15 kg and 15 mL daily for children >15 kg.

In Table 5, the four combination trace element products for pediatrics and neonates have as many as seven trace elements in combination at different doses in the formulations including: zinc, copper, manganese; some with chromium; and most with no selenium or one with 2 mcg per 1 mL, which is Peditrace® that also contains iodine and fluoride. Again, ASPEN 2015 recommends that routine supplementation with iodide, and fluoride could be beneficial, and that the chromium dose should be reduced. However, yet again, Applicant here did not include chromium, iron, iodide, and/or fluoride to their unique formulations in, for example, claim 81.

Regarding selenium, the ASPEN 2015 guidelines recommend 2 mcg per kilogram dosing of selenium and, contrary to the ASPEN 2015 guidelines, Applicant actually increased the dose of selenium to 3 times that amount per kilogram and have a 6 mcg per 1 mL dose of selenium in their unique formulation (see the bolded arrows above in Table 5). See Declaration of Dr. Joseph I. Boullata at Paragraphs 37 and 38.

As far as the combination trace element products in Europe, in Table 9 of ASPEN 2015 (shown below), there were two new combination trace element products that became

available at that time, each having nine trace elements (per 1 mL) and both products contain iron, molybdenum, iodine, and fluoride.

Table 9. Comparison of New Adult Multi-TE Products in Europe (not FDA Approved) and A.S.P.E.N. Recommendations for Multi-TE Products.[21]

		New Unapproved Products	
Trace Elements	A.S.P.E.N. Recommendations (daily dose)	Addaven® (10 mL daily dose)	Nutryelt® (10 mL daily dose)
Zinc (Zn)	No changes (3–5 mg)*	5 mg	10 mg
Copper (Cu)	Decrease to 0.3–0.5 mg	0.4 mg	0.3 mg
Manganese (Mn)	Decrease to maximum of 0.055 mg	0.055 mg	0.055 mg
Chromium (Cr)	10 mcg sufficient for most patients but need product without Cr for patients prone to Cr toxicity	10 mcg	10 mcg
Selenium (Se)	60–100 mcg (dose higher than 60 mcg preferred)	80 mcg	70 mcg
Iron (Fe)	Routine supplementation of PN could be beneficial, but more research is needed especially with lipid containing PN	1.1 mg	1 mg
Molybdenum (Mo)	Insufficient data to recommend routine administration	19 mcg	20 mcg
Iodide (I)	Routine supplementation of PN could be beneficial, but more research is needed	130 mcg	130 mcg
Fluoride (F)	Routine supplementation of PN could be beneficial, but more research is needed	950 mcg	950 mcg
Vial size	....	10-mL single dose	10-mL single dose
Manufacturer	....	Fresenius Kabi (Lake Zurich, IL)	Laboratoire Aguettant (Saint-Fons, France)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; FDA, United States Food and Drug Administration; PN, parenteral nutrition; TE, trace element.
*A.S.P.E.N. recommendations in the original position paper were for no changes in the products currently available in the United States that contained 3–5 mg zinc/day (see Table 4).

Also, for that time, the two newer adult European combination trace element products with nine trace elements in Table 9 have 5 different doses in the formulations including chromium at 1 mcg per 1 mL; selenium at 8 mcg and 7 mcg per 1 mL, and all contain iron, molybdenum, iodine, and fluoride. Therefore, out of the 12 (10 U.S. and 2 Europe) formulations presented in ASPEN 2015 each have different trace elements and different doses. As a result, again, hundreds of different formulations can be made with different combinations of trace elements and different doses per 1 mL.

Notwithstanding ASPEN 2012 and 2015 and their hundreds of combination trace elements and doses per mL, there are no adult formulations that have as active ingredients about 3,000 µg of zinc, about 300 µg of copper, about 60 µg of selenium, and about 55 µg of manganese and no added chromium per 1 mL in an all-in-one trace element combination product as in, for example, claim 1. Also, there are no pediatric or neonatal combination trace element products with as active ingredients about 1000 µg of zinc, about 60 µg of copper, about 6 µg of selenium and about 3 µg of manganese and no added chromium per 1 mL in an all-in-one trace

element combination product as in, for example, claim 81. Therefore, again, what Applicant did was more than routine optimization of a formulation. See Declaration of Dr. Joseph I. Boullata at Paragraphs 39, 40 and 41.

Applicant emphasizes that, similar to ASPEN 2012, ASPEN 2015 also explains that the parenteral multi-trace element preparations that are commercially available in the U.S. provide potentially "toxic amounts of manganese, copper, and chromium (see ASPEN 2015 Abstract) and that **"safer parenteral multi-TE products" need to be developed** (see ASPEN 2015 at Page 563). Therefore, like Burjonrappa and ASPEN 2012, ASPEN 2015 also identifies a long felt and persistent need, without solution, for new and safer combination trace element products for parenteral nutrition. See Declaration of Dr. Joseph I. Boullata at Paragraphs 42 and 43.

The need for new and safer combination trace element products for parenteral nutrition was still unmet so much so that the FDA also had concerns about the currently available trace elements in 2012 and 2015 and warned manufacturers about unapproved drugs in 2020 (see FDA Warning Unapproved Drugs Jan. 29, 2020 -Exhibit F). This long felt need persisted over 8 years until the current application was filed and products containing the claimed combinations of trace elements and their specific doses were approved by FDA. The new combination and doses of trace element products of the current application satisfied this long felt need that Burjonrappa, ASPEN 2012, ASPEN 2015 and the FDA identified.

Moreover, the Tralement® product connected with, for example, claim 1 and the Multrys® product connected with, for example, claim 81 were the first FDA approved combination trace element products that can safely and effectively supplement the trace element needs in a majority of patients. If the new combination and concentration trace element products of the current application were indeed so obvious or so routine, then why did someone else not make them and seek FDA approval before the current application was filed? See Declaration of Dr. Joseph I. Boullata at Paragraphs 43, 44 and 45 and Declaration of Ms. Joann Gioia at Paragraphs 6 and 10.

In summary, previously available combination trace element products were available in various doses and the ASPEN 2012 and ASPEN 2015 recommendations merely present general dosing guidelines for PN patients. However, it is not obvious or routine to: select from

the hundreds of possible formulations and at least 10 elemental components (e.g., zinc, selenium, copper, manganese, chromium, iron, molybdenum, iodine, fluoride, and cobalt); remove some of those 10 components (i.e., chromium, iron, molybdenum, iodine, fluoride, and cobalt); then select specific doses from those hundreds of possible formulations based on various and conflicting doses and conflicting dosage guidelines; and create new combinations of trace element products for adults, pediatric and neonatal patients as in, for example, claims 1 and 81 per 1 mL in all-in-one formulations that did not previously exist in the art, are FDA approved and can be used by a majority of patients. This is especially true considering that ASPEN 2015 explains that iron, iodine and/or fluoride may be beneficial and further considering that chromium 10 mcg is sufficient for most adult patients and selenium doses higher than 60 mcg are preferred. Also, for most neonatal patients, chromium should be reduced and that selenium 2 mcg should be used. Therefore, regarding for example, claims 1 and 81, Applicant did more than routine optimization. They satisfied this persistent and long felt need, and it was not obvious. See Declaration of Dr. Joseph I. Boullata at Paragraphs 42-45.

E. The New Trace Elements Formulations Have Achieved Wide Spread Use and Commercial Success

Applicant submits that these unique combinations and doses of trace elements of the current claims (e.g., claims 1 and 81) not only satisfied a long felt need for safe and effective trace element supplementation that persisted for years in the art, but also achieved wide spread use and commercial success. They were also the first FDA approved combination trace element products that can safely and effectively supplement the trace element needs in a majority of patients. See Declaration of Dr. Joseph I. Boullata at Paragraphs 10, 20, 23, and 43-45 and Declaration of Ms. Joann Gioia at Paragraphs 6-10.

In order to establish commercial success, the patentee must establish that a connection (or nexus) exists between the novel aspects of the patent claim(s) and the alleged commercial success. Where the claimed invention is a unique combination of known elements from the prior art…sales figures alone are also evidence of commercial success. See *Chemours Co. FC, LLC v. Daikin Indus., Ltd.,* 4 F.4th 1378 (Fed. Cir. 2021) and MPEP 716.03(b).

Applicant submits that the unique combinations of trace elements and doses of trace

elements of the current claims led to their commercial success and satisfied a long felt need for safe and effective trace element supplementation. Applicant clearly establishes the connection or nexus between the Tralement® and Multrys® trace element products and the combination of trace elements and specific doses of the current claims. For example, Table A (above) connects the unique combinations and doses of the Tralement® trace element product with that of claim 1. Likewise, Table B (above) connects the unique combinations and doses of the Multrys® trace element product with that of claim 81. See also Declaration of Dr. Joseph I. Boullata at Paragraphs 10-13 and 20-22 and Declaration of Ms. Joann Gioia at Paragraphs 6-10.

Moreover, both Tralement® and Multrys® were the first FDA approved combination trace element products for safe and effective zinc, copper, manganese and selenium supplementation for a majority of adult, pediatric and/or neonatal patients. (See Exhibits G and H- American Regent FDA announcements). See Declaration of Ms. Joann Gioia at Paragraph 6.

While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. See, for example, *Leo Pharms., Inc. v. Rea*, 726 F.3d at 1358. (Fed. Cir. 2013).

Applicant submits that the unique combinations of trace elements and doses of trace elements of the current claims led to their post filing commercial success as evidenced by the yearly gross sales of the Tralement® product connected with, for example, claim 1 and the Multrys® product connected with, for example, claim 81.

For example, the Tralement® product launched in September 2020 and had over $28 million in gross sales in 2020. In 2021, the gross sales of Tralement® increased to over $124 million and in 2022, the gross sales continued to increase to over $125 million. Regarding the Multrys® product, it launched a year later in September 2021 and had over $4 million in gross sales for 2021. In 2022, the gross sales for Multrys® increased to over $14 million. Moreover, the commercial success is not due to any significant marketing effort by American Regent. See Declaration of Ms. Joann Gioia at Paragraphs 11-13.

In summary, Applicant's unique combination and doses of trace elements at the specific dosage ranges are new compositions not known in the cited art. They are not the result of routine optimization, address a long felt commercial need, have wide spread use and post filing commercial success and would not have been obvious to a person of ordinary skill in the art.

Therefore, withdrawal and reconsideration of the rejections of claims 1-18, 65-71, and 74-77 under 35 U.S.C. § 103(a) is respectfully requested.

3. No Disclaimers or Disavowals

Although the present communication may include alterations to the claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited reference. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history may not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

4. Conclusion

No fee is believed to be due with respect to filing this response, except the fee for 24 extra claims and 7 independent claims. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 50-5960 for such sum.

If the Office has any questions regarding the present application, the Office is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,

/William D. Schmidt/
William D. Schmidt
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EXHIBIT G

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

109802 7590 05/24/2023

Sorell, Lenna & Schmidt, LLP
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SUITE 110
Hauppauge, NY 11788

EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/24/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/365,695	07/01/2021	Gopal Anyarambhatla	1848-32 US	8197

TITLE OF INVENTION: TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	08/24/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

109802 7590 05/24/2023
Sorell, Lenna & Schmidt, LLP
135 ENGINEERS ROAD
SUITE 110
Hauppauge, NY 11788

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/365,695	07/01/2021	Gopal Anyarambhatla	1848-32 US	8197

TITLE OF INVENTION: TRACE ELEMENT COMPOSITIONS, METHODS OF MAKING AND USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	08/24/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, ALI	1617	424-630000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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EXAMINER	
SOROUSH, ALI	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 05/24/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/365,695	Applicant(s) Anyarambhatla et al.	
	Examiner ALI SOROUSH	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the response filed on 04/26/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some* c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 12302022, 04262023, 04272023.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

Continuation of 3. The allowed claim(s) is/are: 1-18,56,65-67,70-71 and 74-104

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Acknowledgement of Receipt

Applicant's response filed on 04/26/2023 to the Office Action mailed on 10/26/2022 is acknowledged.

Claim Status

Claims 1-18, 56, 65-67, 70, 71, and 74-104 are pending.

Claims 19, 55, 57-64, and 72 were previously cancelled and claims 56, 68 and 69 are cancelled.

Claim 78-104 are newly added.

Claim 1, 4-6, 8, 9, 13, 16, 17, 65-67, and 74 are currently amended.

Claims 1-18, 56, 65-67, 70, 71, and 74-104 have been examined.

Claims 1-18, 56, 65-67, 70, 71, and 74-104 are rejected.

Priority

Priority to application 63/047708 filed on 07/02/2020 is acknowledged.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 12/30/2022, 04/26/2023, and 04/27/2023 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Withdrawn Claim Rejections - 35 USC § 103

The rejection of claims 68 and 69 under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019) is moot since the claim is cancelled.

The rejection of claim(s) 1-18, 65-67, 70, 71, and 74-77 under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019) is withdrawn in view of the amendments to the claims and Applicant's arguments.

The rejection of claims 68 and 69 under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019) in view of Burjonrappa et al. (Role of trace elements in parenteral nutrition support of the surgical neonate, Published 2012) is moot since the claims.

The rejection of claim(s) 1-18, 65-67, 70, 71, and 74-77 under 35 U.S.C. 103 as being unpatentable over Drugs.com (Multitrace-5, Published 09/07/2015) as evidenced by Americanregent.com (Multitrace 5 Concentrate (Trace Elements Injection 5, USP), Multitrace 5 (Trace Elements Injection 5, USP) Safety Data Sheet, Published 01/09/2019) in view of Burjonrappa et al. (Role of trace elements in parenteral nutrition support of the surgical neonate, Published 2012) is withdrawn in view of the amendments to the claims and Applicant's arguments.

Election/Restrictions

This application is in condition for allowance except for the presence of claim 56 directed to an invention non-elected with traverse in the reply filed on 07/01/2021. Applicant is given **TWO (2) MONTHS** from the date of this letter to cancel the noted claims or take other appropriate action (37 CFR 1.144). Failure to take action during this period will be treated as authorization to cancel the noted claims by Examiner's Amendment and pass the case to issue. Extensions of time under 37 CFR 1.136(a) will not be permitted since this application will be passed to issue.

The prosecution of this case is closed except for consideration of the above matter.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

Claim 56 is cancelled.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: Applicant's showing of unexpected data, wherein the absence of chromium in a trace element composition results in a composition having considerably less silicon impurities when compared to a trace element composition comprising chromium.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached M-F 9:30am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617